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(54) Title: TACHYKININ ANTAGONISTS (57) Abstract The small compounds of the instant invention are tachykinin antagonists. The compounds are highly selective and functional NK ₃ antagonists expected to be useful in the treatment of pain, depression, anxiety, panic, schizophrenia, neuralgia, addiction disorders, inflammatory diseases, gastrointestinal disorders, vascular disorders, and neuropathological disorders.		

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TACHYKININ ANTAGONISTS

5

BACKGROUND OF THE INVENTION

10 Over the last decade, major advances have been
made in the understanding of the biology of the
mammalian tachykinin neuropeptides. It is now well
established that substance-P (1), neurokinin A (NKA)
15 (2), and neurokinin B (NKB) (3), all of which share a
common C-terminal sequence Phe-X-Gly-Leu-Met-NH₂,
(Nakanishi S., Physiol. Rev., 67:117 (1987)), are
widely distributed throughout the periphery and central
nervous system (CNS) where they appear to interact with
at least three receptor types referred to as NK₁, NK₂,
20 and NK₃, (Guard S., et al., Neurosci. Int., 18:149
(1991)). Substance-P displays highest affinity for NK₁
receptors, whereas NKA and NKB bind preferentially to
NK₂ and NK₃ receptors, respectively. Recently, all
three receptors have been cloned and sequenced and
25 shown to be members of the G-protein-linked "super
family" of receptors (Nakanishi S., Annu. Rev.
Neurosci., 14:123 (1991)). A wealth of evidence
supports the involvement of tachykinin neuropeptides in
a variety of biological activities including pain
30 transmission, vasodilation, smooth muscle contraction,
bronchoconstriction, activation of the immune system
(inflammatory pain), and neurogenic inflammation
(Pernow B., Pharmacol. Rev., 35:85 (1983)). However,
to date, a detailed understanding of the physiological
35 roles of tachykinin neuropeptides has been severely
hampered by a lack of selective, high affinity,

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metabolically stable tachykinin receptor antagonists that possess both good bioavailability and CNS penetration. Although several tachykinin receptor antagonists have been described (Tomczuk B.E., et al.,
5 Current Opinions in Therapeutic Patents, 1:197 (1991)), most have been developed through the modification and/or deletion of one or more of the amino acids that comprise the endogenous mammalian tachykinins such that the resulting molecules are still peptides that possess
10 poor pharmacokinetic properties and limited in vivo activities.

However, since 1991, a number of high-affinity nonpeptide antagonists have been reported. Snider R.M., et al., (Science, 251:435 (1991)), and
15 Garret C., et al., (Proc. Natl. Acad. Sci., 88:10208 (1991)), described CP-96,345 and RP 67580, respectively, as antagonists at the NK₁ receptor, while Advenier C., et al., (Brit. J. Pharmacol., 105:78
20 (1992)), presented data on SR 48969 showing its high affinity and selectivity for NK₂ receptors. More recently Macleod, et al., (J. Med. Chem., 36:2044 (1993)) have published on a novel series of tryptophan derivatives as NK₁ receptor antagonists. It is of
25 interest that most of the nonpeptide tachykinin receptor antagonists described to date arose, either directly or indirectly, out of the screening of large compound collections using a robust radioligand binding assay as the primary screen. Recently, FK 888, a
30 "dipeptide" with high affinity for the NK₁ receptor was described (Fujii J., et al., Neuropeptide, 22:24 (1992)).

International Publication Numbers WO 93/01169, WO 93/01165, and WO 93/001160 cover certain nonpeptide tachykinin receptor antagonists.

35 NK_B and also NK₃ receptors are distributed throughout the periphery and central nervous system

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(Maggi, et al., J. Auton. Pharmacol., 13:23 (1993)). NKB is believed to mediate a variety of biological actions via the NK₃ receptor including gastric acid secretion; appetite regulation; modulation of
5 serotonergic, cholinergic, and dopaminergic systems; smooth muscle contraction and neuronal excitation. Recent publications descriptive of this art include Polidor, et al., Neuroscience Letts., 103:320 (1989);
Massi, et al., Neuroscience Letts., 92:341 (1988), and
10 Improta, et al., Peptides, 12:1433 (1991). Due to its actions with dopaminergic (Elliott, et al., Neuropeptides, 19:119 (1991)), cholinergic (Stoessl, et al., Psycho. Pharmacol., 95:502 (1988)), and
serotonergic (Stoessl, et al., Neuroscience Letts.,
15 80:321 (1987)) systems, NKB may play a role in psychotic behavior, memory functions, and depression.

Accordingly, compounds capable of antagonizing the effects of NKB at NK₃ receptors will be useful in
treating or preventing a variety of disorders including
20 pain, depression, anxiety, panic, schizophrenia, neuralgia, addiction disorders, inflammatory diseases; gastrointestinal disorders including colitis, Crohn's disease, inflammatory bowel disorder, and satiety;
vascular disorders such as angina and migraine and
25 neuropathological disorders such as Parkinsonism and Alzheimer's.

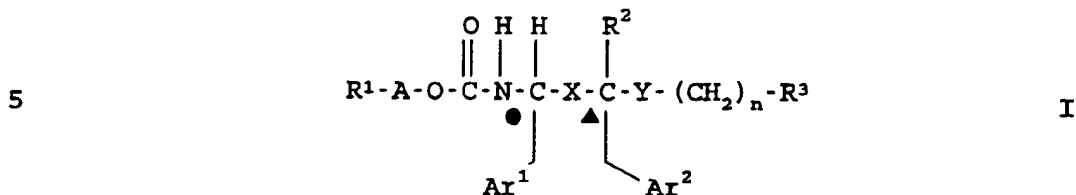
SUMMARY OF THE INVENTION

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The invention covers tachykinin antagonists. The compounds of the invention have been proved to be highly selective and functional NK₃ antagonists.

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Compounds of the invention are those of formula



or a pharmaceutically acceptable salt thereof wherein:

10 R^1 is hydrogen,

OR^4 ,

CO_2R^4 ,

cyclo- or polycycloalkyl of from 4 to 10 carbons

with from 0 to 3 substituents selected from:

15 alkyl,

halogen,

$(\text{CH}_2)_m\text{CO}_2\text{R}^4$,

$(\text{CH}_2)_m\text{OR}^4$ wherein m is an integer of
from 1 to 6 and R^4 is hydrogen or
20 alkyl, or

phenyl unsubstituted or substituted by from 1 to

3 groups selected from:

alkyl,

halogen,

25 nitro,

CF_3 ,

$(\text{CH}_2)_p\text{OR}^6$,

$(\text{CH}_2)_p\text{CO}_2\text{R}^6$,

$(\text{CH}_2)_p\text{NR}^6\text{R}^7$ wherein p is an integer of
from 0 to 6 and R^6 and R^7 are each
independently hydrogen or alkyl;

30

A is $-(\text{CH}_2)_q(\text{C}(\text{CH}_3)_2)_r(\text{CH}_2)_s-$ wherein q, r, and s are
integers of from 0 to 6, 0 to 1, and 0 to 6,
respectively;

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Ar¹ and Ar² are each independently phenyl unsubstituted
or substituted with from 1 to 3 substituents
selected from:

alkyl,
5 halogen,
nitro,
CF₃,
(CH₂)_tOR⁶,
(CH₂)_tCO₂R⁶, or
10 (CH₂)_tNR⁶R⁷ wherein t is an integer of from
0 to 6 and R⁶ and R⁷ are each
independently hydrogen or alkyl;

X and Y are each independently

-CONH-,
15 -CONCH₃-,
-COO-,
-CH₂NH-,
-NHCO-,
-CH₂O-,
20 -COCH₂-, or
-CH₂CH-;

n is an integer of from 0 to 10; and

R³ is hydrogen,

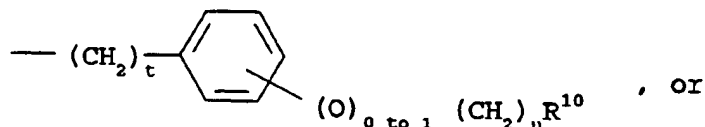
straight or branched alkyl of from 3 to 10 carbons
25 with from 0 to 3 substituents selected from:

(CH₂)_nOR⁸,
CO₂R⁸,
-NHCOCH₃,
-NR⁸R⁹,
30 -SO₂Me,
-SOMe,
-SO₂NH₂,
-CONR⁸R⁹,
-NHCONR⁸R⁹,
35 -COR⁴ wherein n is an integer of from
0 to 6, R⁴ is as above, R⁸ and R⁹

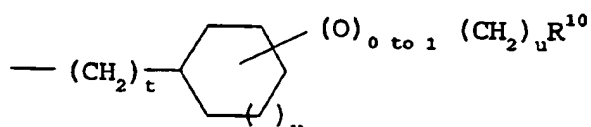
-6-

are each independently hydrogen or
alkyl,
-guanidine,
-amidine,

5 R^3 is also



10



15 wherein t is an integer of from 0 to 5, v is
an integer of from 0 to 2, u is an
integer of from 0 to 4, and R^{10} is
hydrogen, hydroxy, alkoxy, COOH,
CO₂alkyl, CONR⁸R⁹, NHCONR⁸R⁹ guanidine or
amidine.

20 All stereoisomers are considered (*,▲).

Preferred compounds of this invention are those of
Formula I above wherein

R^1 is hydrogen,

OR⁴,

25 CO₂R⁴ wherein R^4 is hydrogen, methyl, or ethyl,
cycloalkyl of from 4 to 8 carbons,
bicycloalkyl of 10 carbons,
tricycloalkyl of 10 carbons, or
phenyl;

30 A is $-(CH_2)_q(C(CH_3)_2)_r(CH_2)_s-$ wherein q , r , and s are
integers of from 0 to 2, 0 to 1, and 0 to 4,
respectively;

Ar^1 and Ar^2 are each independently phenyl unsubstituted
or mono- or disubstituted by:

35 alkyl,
halogen,

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CF₃,
 NO₂, or
 NH₂;

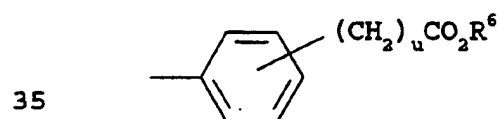
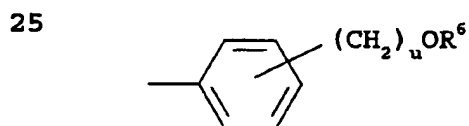
X and Y are each independently

5 -CONH-,
 -CONCH₃-,
 -CO₂-, or
 -CH₂NH-;

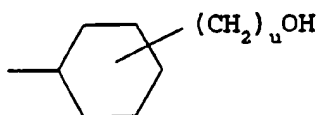
n is an integer of from 0 to 9; and

10 R³ is hydrogen,
 straight, branched, or cyclic alkyl of from 3 to
 10 carbons with from 0 to 3 substituents
 selected from:

15 OH,
 OCH₃,
 CO₂R⁸,
 NHCOCH₃,
 NR⁸R⁹,
 CONR⁸R⁹,
 NHCONR⁸R⁹ wherein R⁸ and R⁹ are each
 independently selected from
 hydrogen and methyl, or
 COCH₃,

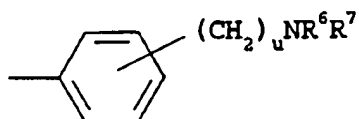


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, or

5



wherein u is an integer of from 0 to 4 and R^6 and
 10 R^7 are each independently selected
 from hydrogen and methyl.

Preferred stereoisomers are when \bullet is S and \blacktriangle is R.

More preferred compounds of this invention are
 those of Formula I above wherein:

15 R^1 is hydrogen,

OR⁴,

CO₂R⁴ wherein R⁴ is hydrogen or methyl,
 cycloalkyl of from 5 to 7 carbons;

20 A is $-(CH_2)_q(C(CH_3)_2)_r(CH_2)_s-$ wherein q , r , and s are
 integers of from 0 to 3, 0 to 1, and zero,
 respectively;

Ar¹ and Ar² are each independently phenyl unsubstituted
 or mono- or disubstituted by:

alkyl,

25 chloro, or

CF₃;

X and Y are each independently

-CONH-,

-CONCH₃-,

30 -CO₂-, or

-CH₂NH-;

n is an integer of from 0 to 9; and

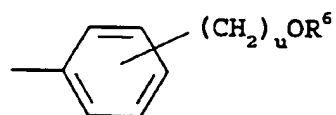
R³ is hydrogen,

straight, branched, or cycloalkyl of from 3 to
 35 10 carbons with from 0 to 3 substituents
 selected from:

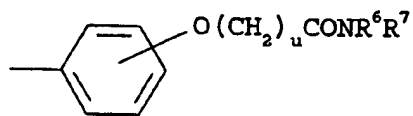
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OH,
 OCH₃,
 CO₂R⁸,
 CONR⁸R⁹, or
 NHCONR⁸R⁹,

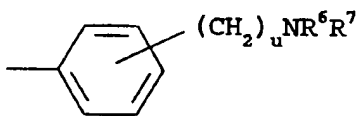
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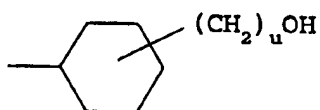


15



, or

20



wherein u is an integer of from 0 to 3, R^6 and R^7
 are each independently hydrogen and methyl,
 R^8 and R^9 are each independently hydrogen and
 methyl.

25

Preferred stereoisomers are when \bullet is S and \blacktriangle is R.

Still more preferred compounds of the invention
 are when:

30

R^1 is cyclohexane,

cyclopentane,

methylcyclohexane,

methylcyclopentane,

phenylethyl,

35

t-butyl,

2,2-dimethylpropane, or

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2,2-dimethylpentane;

A when q, r and s are zero;

Ar¹ and Ar² are each phenyl;

5 X and Y are each independently selected from -CONH- and
-CH₂NH-;

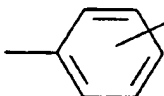
n is an integer of from 3 to 8;

R³ is straight, branched, or cycloalkyl of from 3 to
9 carbons with 1 substituent selected from:

10 OH,
-OCH₃,
-CONR⁸R⁹,
-NHCONR⁸R⁹,

15  O(CH₂)_uCONR⁸R⁹

, or

20  (CH₂)_uOH

wherein u is an integer of from 0 to 3 and R⁸ and
R⁹ are each independently selected from
25 hydrogen and methyl.

Especially preferred examples of the invention
are:

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-
carbonyl]-L-phenylalanyl-N-(8-hydroxyoctyl)-α-methyl-;

30 D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-
carbonyl]-L-phenylalanyl-N-(9-amino-9-oxononyl)-
α-methyl-, trifluoroacetate (10:7) salt;

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-
carbonyl]-L-phenylalanyl-N-[4-(4-methoxyphenyl)butyl]-
35 α-methyl-;

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DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-[3-(4-hydroxyphenyl)propyl]- α -methyl-;

5 DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl- α -methyl-N-3-methylbutyl-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl- α -methyl-N-(5-phenylpentyl)-;

10 DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-cyclopentyl- α -methyl-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-(8-methoxyoctyl)- α -methyl-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-(7-carboxyheptyl)- α -methyl-;

15 DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-[2-(acetylamino)ethyl]- α -methyl-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-(2-cyclopentylethyl)- α -methyl-;

20 DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-[2-(4-chlorophenyl)ethyl]- α -methyl-;

25 DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-[(4-carboxycyclohexyl)-methyl]- α -methyl-, trans-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(4-hydroxyphenyl)acetyl]-L-phenylalanyl- α -methyl-;

30 DL-Phenylalaninamide, N-[(cyclohexylmethoxy)-carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(2-methylpropoxy)-carbonyl]-L-phenylalanyl- α -methyl-;

35 DL-Phenylalaninamide, N-[[3,4-dichlorophenyl)-methoxy]carbonyl]-L-phenylalanyl- α -methyl-;

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DL-Phenylalaninamide, N-[[[octahydro-2-naphthalenyl)oxy]carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-3-chloro- α -methyl-;

5 D-Phenylalaninamide, 3-chloro-N-[(1,1-dimethylethoxy)carbonyl]-DL-phenylalanyl- α -methyl-;

Carbamic acid, [2-[[2-amino-2-oxo-1-(phenylmethyl)ethyl]amino]-1-(phenylmethyl)ethyl]-, 1,1-dimethylethyl ester;

10 D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl-N-[7-[(aminocarbonyl)-amino]heptyl]- α -methyl-;

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl- α -methyl-N-[8-(methylsulfonyl)octyl]-;

name missing; and

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-carbonyl]-L-phenylalanyl- α -methyl-N-[9-(methyldamino)-2-oxononyl]-.

20 Pharmaceutical compositions of therapeutically effective amounts of one or more compounds of Formula I and a pharmaceutically acceptable carrier as useful in treating central nervous system disorders such as but not limited to pain, anxiety, depression, and

25 schizophrenia, panic, addiction disorders.

The compounds are also expected to be useful in treating gastrointestinal diseases including but not limited to colitis, Crohn's disease, inflammatory bowel disorder, and satiety.

30 The compounds are also expected to be useful in treating respiratory disorders such as but not limited to asthma.

The compounds are also expected to be useful in treating inflammation.

35 The compounds are also expected to be useful in treating circulatory insufficiencies.

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DETAILED DESCRIPTION

5 The compounds of Formula I are further defined as follows.

The term "alkyl" means a straight or branched hydrocarbon having from 1 to 12 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, 10 n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl, undecyl, dodecyl, and the like unless stated specifically otherwise.

The term "cycloalkyl" means a saturated hydrocarbon ring which contains from 3 to 12 carbon 15 atoms, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl except as otherwise specifically stated.

The term "polycycloalkyl" means two or more rings as defined above for cycloalkyl such as adamantyl, 20 norbornyl, and bornyl except as otherwise specifically stated.

The term "halogen" is chlorine, fluorine, bromine, or iodine.

25 The compounds of Formula I are capable of forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from 30 nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, 35 alkanedioic acids, aromatic acids, aliphatic and

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aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., "Pharmaceutical Salts," J. of Pharma. Sci., 66:1 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. Preferably, a peptide of Formula I can be converted to an acidic salt by treating with an aqueous solution of the desired acid, such that the resulting pH is less than four. The solution can be passed through a C18 cartridge to absorb the peptide, washed with copious amounts of water, the peptide eluted with a polar organic solvent such as, for example, methanol, acetonitrile, aqueous mixtures thereof, and the like, and isolated by concentrating under reduced pressure followed by lyophilization. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

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Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N'-dibenzylethylenediamine, chloro-procaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge S.M., et al., supra).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. Preferably, a peptide of Formula I can be converted to a base salt by treating with an aqueous solution of the desired base, such that the resulting pH is greater than nine. The solution can be passed through a C18 cartridge to absorb the peptide, washed with copious amounts of water, the peptide eluted with a polar organic solvent such as, for example, methanol, acetonitrile, aqueous mixtures thereof, and the like, and isolated by concentrating under reduced pressure followed by lyophilization. The free acid form may be regenerated by contacting the salt form with an acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

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Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R(D) or S(L) configuration. The present invention includes all enantiomeric and epimeric forms as well as the appropriate mixtures thereof.

The compounds of the instant invention are highly selective and competitive antagonists of the NK₃ receptor.

Compounds have been tested in the in vitro peripheral guinea pig ileum assay and the central guinea pig medial habenula paradigm (see Table I).

TABLE I. NK₃ Antagonist Activity

Example	Guinea Pig Medial Habenula	Guinea Pig Ileum
	(K _e , nM)	(K _B , nM)
1	54	40
2	25	10

The protocols for these two in vitro functional assays are described below. For the guinea pig medial habenula assay, extracellular recordings were made from guinea pig medial habenula neurones in a brain slice preparation in vitro. Compounds were tested for the ability to block senktide-induced increases in firing rate. Parallel shifts to the right of the senktide dose-response curve with no reduction in maximum were taken as an indication of competitive antagonism. Equilibrium constant (K_e) values for the antagonism were obtained from separate experiments and yielded the mean K_e values shown in the final column. None of the compounds tested had any effect on basal neuronal firing rates.

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The experimental procedure for the guinea pig ileum assay is as follows.

Noncumulative concentration-response curves to the selective NK₁ agonist (Met-O-Me¹¹) substance P (substance P-methyl ester, SPOMe) were constructed by addition of increasing doses (≤10 μL) to the organ bath. To assess the effect of putative antagonists, concentration-response curves to the agonist were obtained in the absence, and then the presence of known concentrations of the presumptive antagonist. Contractile responses to SPOMe were expressed as a percentage of the maximum response for the one preparation, and concentration-response data fitted by a least-squares iterative method in Inpolot (Graphpad Software, Inc.) to the logistic function

$$R = 100 \cdot x^n / (EC_{50}^n + x^n)$$

where R is the response, x is the agonist concentration, EC₅₀ is the "location parameter" for the curve (approximates to the value for EC₅₀, the concentration of agonist producing 50% of the maximum response), and n is the "slope factor" of the curve. The effect of the antagonist was observed as a rightward shift of the log(concentration) - response curve, and generally this was quantified in terms of the "dose ratio" (DR) between [EC₅₀]_A and [EC₅₀]_C, these parameters being the measures made in the presence and absence of antagonist, respectively. By repeating estimates for DR using at least three observations at any one concentration of antagonist, and not less than three concentrations of antagonist, the affinity of the antagonist was derived by Schild analysis by plotting log(DR-1) agonist -log[antagonist]. The plots were analyzed by regression analysis, and if the slope of the line of best fit was not significantly different from unity, the intercept on the abscissa from the regression analysis with the slope constrained to unity

-18-

was taken as the negative logarithm of K_B (pK_B), the estimate of the antagonist dissociation constant.

The compounds of the invention were also evaluated in an NK_3 receptor binding assay which is described below.

Chinese hamster ovary cell membranes were prepared on day of use by thawing cells, diluting with culture medium, and centrifuging at 1000 g for 4 minutes. The resulting pellet was resuspended in assay buffer (50 mM Tris, pH 7.4 containing 3 mM $MnCl_2$, 0.02% BSA, 40 μ g/L bacitracin, 2 μ g/mL chymostatin, 2 μ M phosphoramidon, and 4 μ g/mL leupeptin), and washed by centrifugation as above. The cells were then resuspended in assay buffer, counted, and volume adjusted as appropriate. The cell suspension was homogenized using a Brinkman polytron (setting 6, 3 x 10s) and the equivalent of 0.2-0.25 million cells added per tube. For competition studies, membranes were incubated with [125 I]-[MePhe⁷]neurokinin B (40-100 pM) in the presence and absence of test compounds for 90 minutes at 22°C. Assays were terminated by filtration under vacuum using a Brandel harvester onto GF/C filters presoaked with 0.1% PEI for at least 2 hours, and cpm bound determined using a gamma counter. In all cases, specific binding was defined by 1 μ M senktide.

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TABLE II. In Vitro NK₃ Receptor Binding Data

Example		Binding IC ₅₀ (nM)
5	1	40
	2	20
	3	83
	4	88
	5	123
10	6	77
	7	556
	8	102
	9	229
	10	180
15	11	129
	12	141
	13	719
	14	1520
	15	5890
20	16	1220
	17	1310
	18	1530
	19	3060
	20	1350
25	21	904
	22	4330
	23	16
	24	21
	25	69
30	26	21

DESCRIPTION OF SYNTHETIC SCHEMES

Schemes 1 through 3 describe the synthesis of intermediates required for the preparation of the final compounds as found in the examples.

In Scheme 1 the BocPhe α MePheOH intermediate is prepared by active ester coupling of the acid Boc(s)Phe to either R or S isomers of α MePheOMe followed by base catalyzed hydrolysis. The methyl ester α MePheOMe is synthesized from the readily available acid via the use of thionyl chloride and methanol.

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The synthesis of the amine Intermediates III and IV are described in Scheme 2. Conversion of the readily available 9-bromo-1-nonanol to the corresponding amino acid was achieved via initial
5 oxidation of the alcohol to the acid using concentrated nitric acid followed by displacement of the bromine by azide and subsequent conversion of the azide to the amine via catalytic hydrogenation. Protection of the amine with a Boc group followed by protection of the
10 acid in the form of a methyl ester gave, after acid catalyzed deprotection of the Boc group, the required amino acid methyl ester Intermediate III. Intermediate IV was similarly prepared via azide displacement of the bromine atom in 8-bromo-1-octanol
15 followed by catalytic reduction of the azide group to an amine.

Scheme 3 describes the synthesis of Intermediate V which is a 4-aryl butylamine derivative. Friedel-Crafts acylation of anisole with succinic anhydride
20 yielded a γ -keto acid which was subsequently reduced to give an aryl alkyl acid derivative. This was converted to Intermediate V via the amide followed by reduction with borane methyl sulfide complex.

The synthesis of Examples 1 through 3 are
25 described in Scheme 4. Active ester coupling of the acid Intermediate I with the amine Intermediates IV and V gave Examples 1 and 3, respectively. Example 2 was prepared starting from Intermediate I via initial active ester coupling with Intermediate III followed
30 by base hydrolysis of the methyl ester to the corresponding acid and finally conversion to the target amide via active ester methodology.

Schemes 5 and 6 describe the synthesis of further intermediates listed as Intermediates VI to IX. Amine
35 Intermediates VI and VII, 5-phenyl-1-pentylamine and cyclopentylethylamine, were prepared from their

-21-

corresponding alcohols via conversion of the alcohol to the tosylate followed by displacement of the tosylate by azide and reduction of the azide to the target amines VI and VII. Intermediates VIII and IX were both prepared from N-Boc protected 8-amino-1-octanoic acid which in turn was prepared from readily available 8-amino-1-octanoic via a Schotten-Baumen acylation. Conversion of the acid of N-Boc-8-amino-1-octanoic acid to the alcohol followed by methylation using trimethylsilyl diazomethane yielded, after acid catalyzed removal of the Boc group, Intermediate VIII. Esterification of the acid group in N-Boc-8-amino-1-octanoic acid using active ester methodology followed by acid catalyzed removal of the Boc group gave Intermediate IX.

The synthesis of Examples 4 through 13 are described in Scheme 7. The central starting material for these syntheses was Boc(S)Phe(RS) α MePheOH. Examples 4 through 8 are prepared from the central intermediate by active ester coupling to 3-(4-hydroxyphenyl)propylamine, 3-methylbutylamine, 5-phenyl-1-pentylamine, cyclopentylamine, and Intermediate III, respectively. Example 9 is synthesized via active ester mediated coupling of Intermediate IX to the acid intermediate followed by base catalyzed hydrolysis to yield the desired acid. Finally, Examples 10 through 13 were prepared via active ester coupling of the acid intermediate to N-acetylenediamine, cyclopentylethylamine (VII), 2-(4-chlorophenyl)ethylamine, and trans-4-(aminomethyl)cyclohexane carboxylic acid, respectively.

In Scheme 8, Example 14 is prepared from α MePhe via initial N-Boc protection, preparation of the amide via active ester methodology, acid catalyzed removal of the N-Boc group, and finally coupling to Boc(S)PheOpfp. Removal of the N-Boc group with TFA gave an amine

-22-

intermediate, (S)Phe(RS) α MePheNH₂, from which Examples 15 and 16 were prepared via active ester coupling to 4-hydroxyphenyl acetic acid and addition to cyclohexyl methyl chloroformate, respectively.

5 In Scheme 9, Examples 17 and 18 were prepared by the addition of isobutyl chloroformate and 3,4-dichlorobenzylchloroformate, respectively, to the amine intermediate (XII). Intermediate XII was, in turn, prepared from TFA(RS) α MePheNH₂ via coupling to
10 Fmoc(S)PheOpfp followed by piperidine catalyzed deprotection of the Fmoc group.

 The synthesis of Example 19 is described in Scheme 10. Base promoted coupling of the p-nitrophenyl carbonate of decahydro-2-naphthol to the amine
15 Intermediate XII yielded the desired carbamate derivative Example 19.

 Scheme 11 describes the synthesis of Examples 20 and 21. Example 20 is derived from m-chlorophenyl-alanine methyl ester and is synthesized via initial
20 N-Boc protection, hydrolysis of the methyl ester to the corresponding carboxylic acid followed by active ester coupling of the acid group to Intermediate XI, TFA(R) α MePheNH₂. Example 21 is synthesized starting
25 from α -methyl-m-chlorophenyl alanine which is then coupled, using to active ester methodology, to Boc(S)Phe and the methyl ester converted to the amide in Example 21 via base catalyzed hydrolysis to the acid followed by active ester ammonolysis.

 The synthesis of the aminomethylene amide bond isostere derivative, Example 22, is described in
30 Scheme 12. The starting material for this synthesis is N-Boc protected phenylalaninol. This is then oxidized using Swern conditions to the aldehyde which is consequently reductively coupled to (S)phenyl-alaninamide to yield Example 22.
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The synthesis of the compound of Example 23 is described in Scheme 13.

5 Reduction of the in situ generated unsymmetrical anhydride of the carboxylic acid derivative (1) with LiBH_4 in THF gave the alcohol (2). Removal of the nitrogen protecting Boc group of this compound with TFA gave the TFA salt (3). This was subsequently coupled to Boc(S)Phe(R) α MePhe using active ester methodology to give the amide (4). The C-terminal alcohol moiety of
10 this compound was converted to its corresponding azide (6) via preparation of the tosylate using TsCC and base in dichloromethane followed by subsequent displacement with NaN_3 . The azide was catalytically reduced over Lindlar catalyst to give the amide (7), which was then
15 converted to the target urea (8) by reaction with trimethylisocyanate in THF.

The synthesis of the compound of Example 24 is described in Scheme 14.

20 Conversion of the alcohol moiety of (1) into its corresponding tosylate (2) was achieved by reaction with TsCC in dichloromethane and triethylamine/DMAP. Subsequent reaction of the tosylate with methanethiol and K_2CO_3 in DMF gave the thioether (3). This was oxidized by using MCPBA in dichloromethane to yield the
25 target sulphane (4).

The synthesis of the compound of Example 25 is described in Scheme 15.

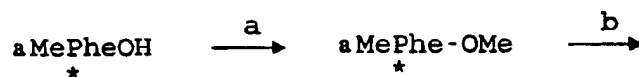
30 Phenol O-alkylation of (1) with bromoacetamide and K_2CO_3 in butan-2-one gave the ether (2). The alkyl alcohol moiety of (2) was then converted to its chloro analogue (3) by reaction with TsCC and pyridine in dichloromethane. Subsequent reaction with NaN_3 in DMF gave the azide (4), which was catalytically reduced over Lindlar catalyst to give the amine (5). This was
35 then coupled to Boc(S)Phe(R) α MePhe using active ester methodology to yield the target amide (6).

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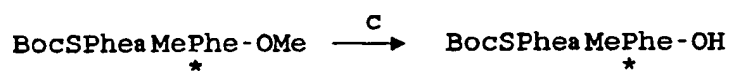
INTERMEDIATES

SCHEME 1

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(I) * = R
(II) * = RS

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- a) SOCl_2 , MeOH;
b) BocSPhe, HBTU, DIPEA, DMF;
c) 1 M LiOH, dioxan.

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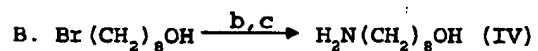
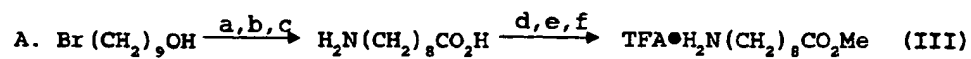
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SCHEME 2

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- a) Concentrated HNO_3 ;
- b) NaN_3 , DMF, $80-90^\circ\text{C}$;
- c) Lindlar catalyst, H_2 , 30°C , 50 psi;
- 15 d) Boc_2O , 1 M NaOH, Na_2CO_3 , dioxan;
- e) DCC, MeOH;
- f) TFA, DCM;

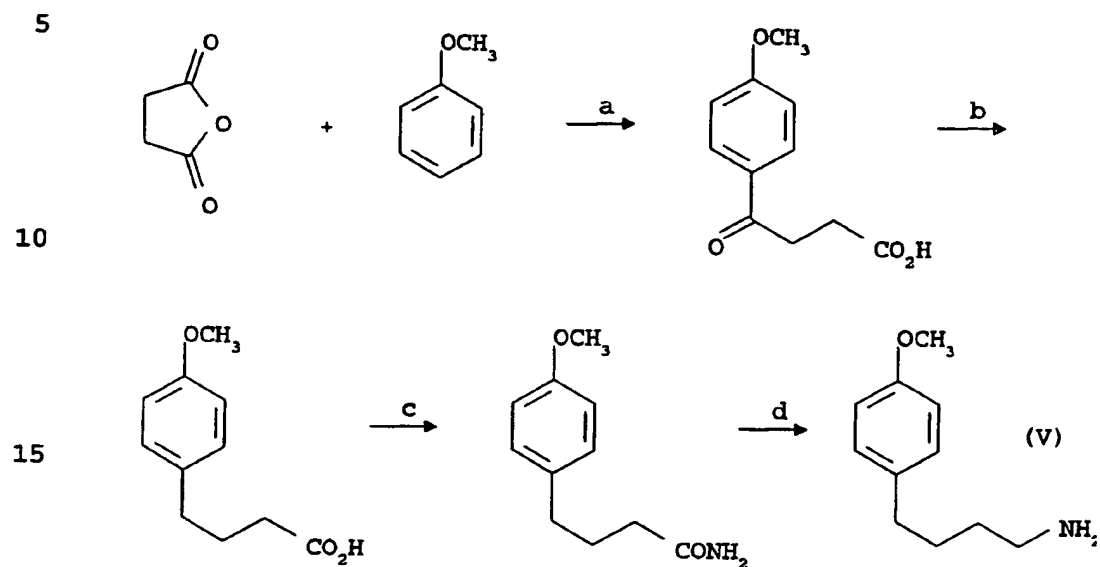
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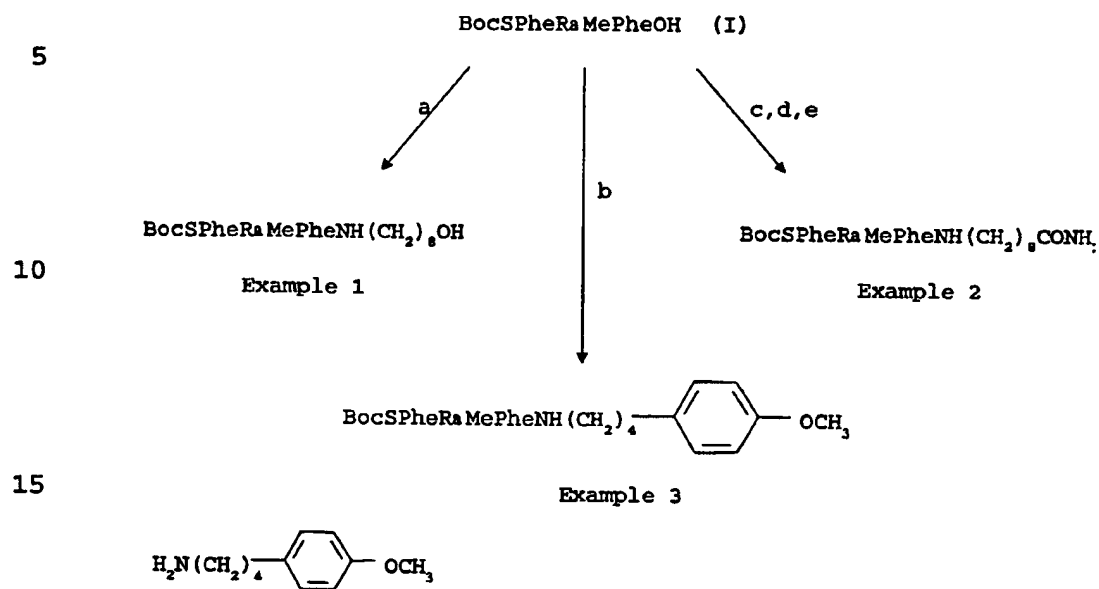
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SCHEME 3a) AlCl_3 , EtNO_2 ;b) KOH , N_2H_4 , DEG ;c) i) EtOCOCN , Et_3N , EtOAc ; ii) NH_3 (g), DMF d) BMS , THF .

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SCHEME 4

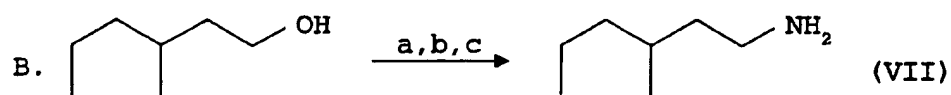
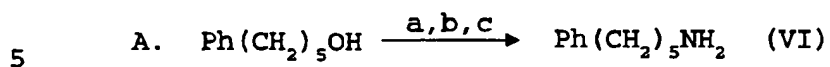
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- 25
- a) i) DCC, HOBt, DMAP, DMF; ii) $\text{H}_2\text{N}(\text{CH}_2)_8\text{OH}$ (IV);
- b) i) HBTU, DIPEA, DMF; ii) $\text{H}_2\text{N}(\text{CH}_2)_4$ (V);
- c) i) HBTU, DIPEA, DMF; ii) $\text{H}_2\text{N}(\text{CH}_2)_8\text{CO}_2\text{Me}$ (III);
- d) 1 M LiOH, dioxan;
- e) i) DCC, pentafluorophenol, DCM; ii) $\text{NH}_3(\text{g})$, DCM.

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SCHEME 5

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a) Tosyl chloride, pyridine;

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b) NaN_3 , DMF;

c) Lindlar catalyst, H_2 , 30°C , 40 psi.

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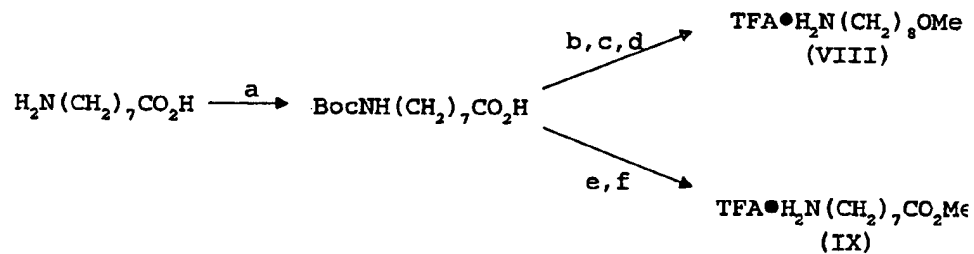
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SCHEME 6

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- a) Boc₂O, 1 M NaOH, dioxan, Na₂CO₃;
- b) i) EtOCOC₂H₅, NMM; ii) LiBH₄, THF;
- c) Fluoroboric acid, DCM, TMSCHN₂;
- d) TFA, DCM;
- e) DCC, MeOH, DMF;
- f) TFA, DCM.

20

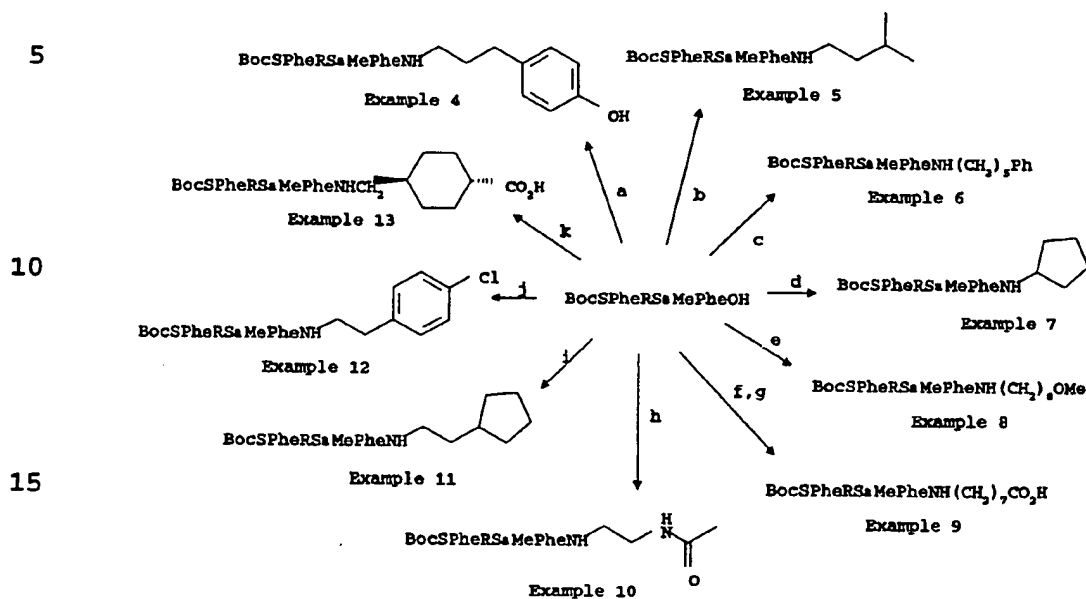
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SCHEME 7

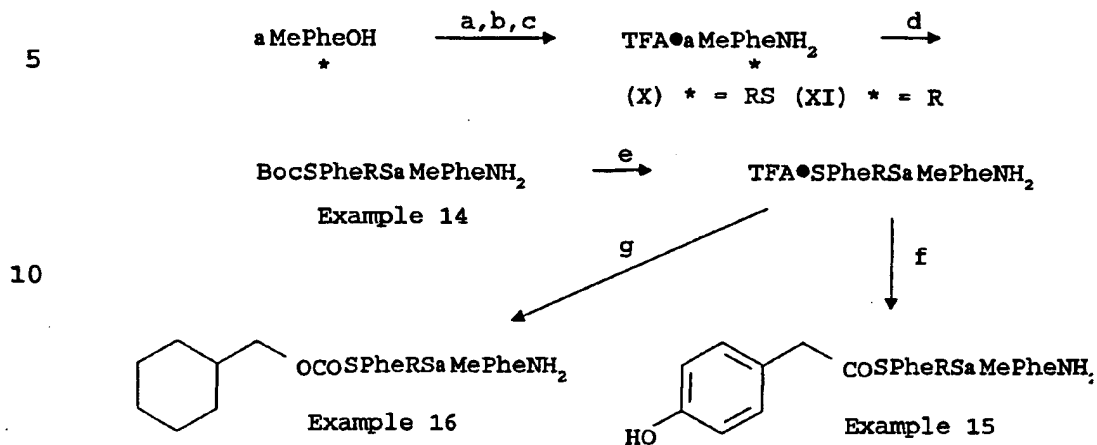


- 20 a) i) HBTU, DIPEA, DMF; ii) 3-(4-hydroxyphenyl)-propylamine;
- b) i) DCC, HOBT, EtOAc; ii) 3-methylbutylamine;
- c) i) DCC, HOBT, EtOAc; ii) $\text{NH}_2(\text{CH}_2)_5\text{Ph}$ (VI);
- 25 d) i) DCC, HOBT, EtOAc; ii) cyclopentylamine;
- e) i) HBTU, DIPEA, DMF; ii) $\text{TFA}\cdot\text{H}_2\text{N}(\text{CH}_2)_8\text{OMe}$ (III);
- f) i) HBTU, DIPEA, DMF; ii) $\text{TFA}\cdot\text{H}_2\text{N}(\text{CH}_2)_7\text{CO}_2\text{Me}$ (IX);
- g) 1 M LiOH, dioxan;
- h) i) HBTU, DIPEA, DMF; ii) N-actylethylenediamine;
- 30 i) i) HBTU, DIPEA, DMF; ii) cyclopentylethylamine (VII);
- j) i) HBTU, DIPEA, DMF; ii) 2-(4-chlorophenyl)-ethylamine
- k) i) HBTU, DIPEA, DMF; ii) trans-4-(aminomethyl)-cyclohexane carboxylic acid.

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SCHEME 8



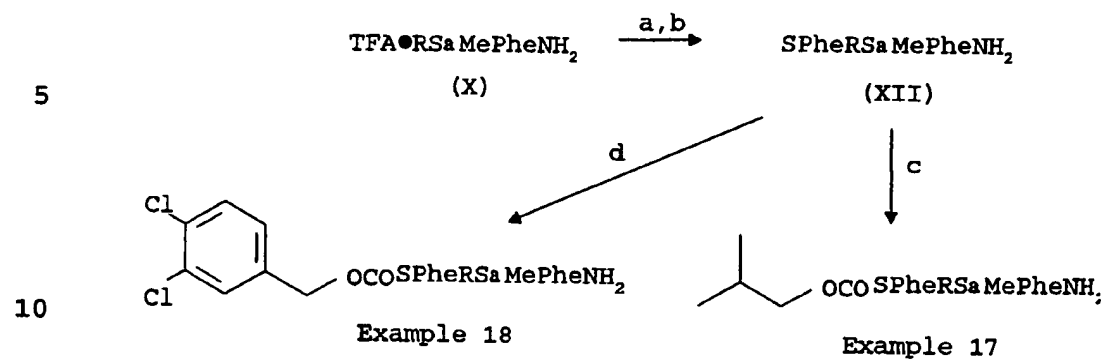
- 20 a) Boc_2O , 10% Na_2CO_3 , dioxan;
b) i) HOBt , DCC , DMF , ii) $\text{NH}_3(\text{g})$;
c) TFA ;
d) BocPheOpfp , Et_3N , EtOAc ;
e) TFA ;
f) i) HBTU , DIPEA , DMF ; ii) 4-hydroxyphenylacetic acid;
25 g) i) cyclohexyl methanol, triphosgene, pyridine, DCM ;
ii) Et_3N , DMF .

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SCHEME 9

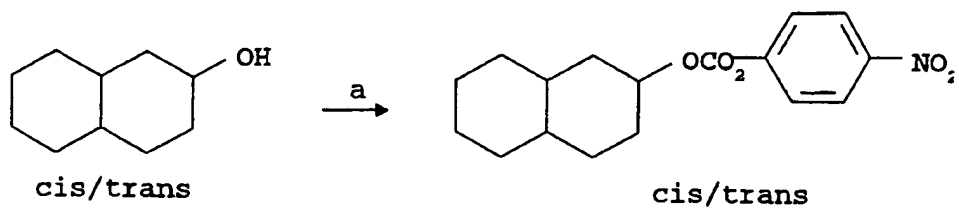


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- 20
- 25
- 30
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- a) Fmoc PheOpfp, Et_3N , DMF;
 - b) 20% piperidine, DMF;
 - c) Isobutyl chloroformate, Et_3N , EtOAc;
 - d) i) 3,4-dichlorobenzylalcohol, triphosgene, pyridine, DCM; ii) Et_3N , EtOAc.

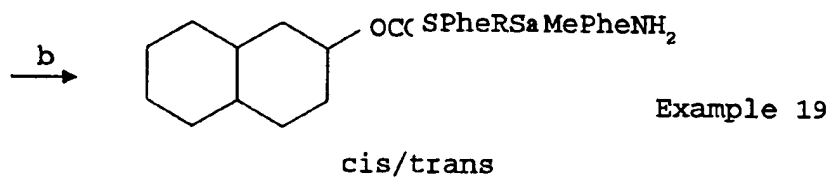
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SCHEME 10

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- a) 4-nitrophenylchloroformate, DCM, pyridine;
20 b) TFA•SPheRSMePheNH₂ (XII), Et₃N, DMF.

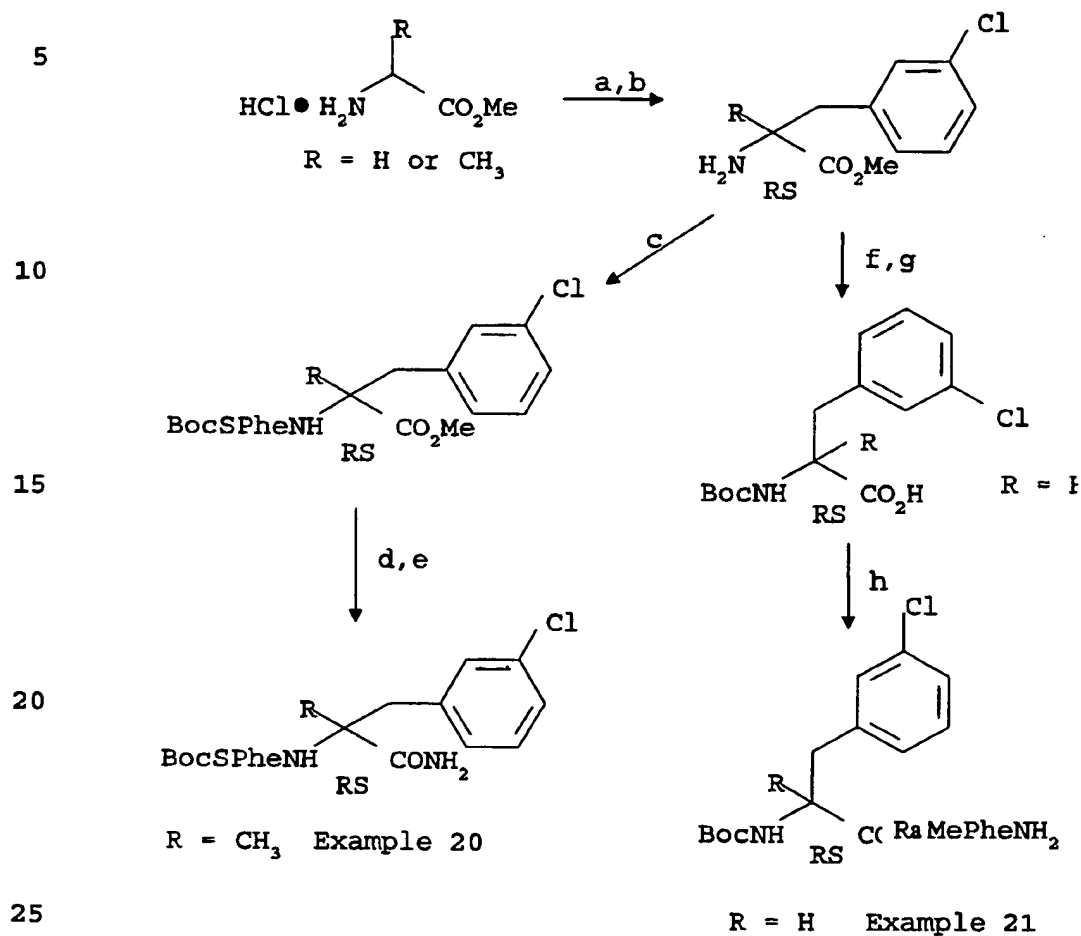
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SCHEME 11

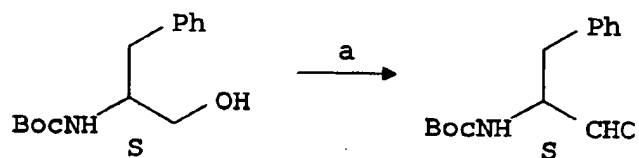


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- a) p-chlorobenzaldehyde, NEt_3 , MgSO_4 , DCM;
- b) i) LHMDS, THF; ii) 3-chlorobenzylbromide;
- 30 iii) HCl, H_2O ; iv) Na_2CO_3 ;
- c) BocPheOH, HBTU, DIPEA, DMF;
- d) 1 M, LiOH, THF/ H_2O ;
- e) i) HOBt, DCC, EtOAc; ii) $\text{NH}_3(\text{aq})$;
- f) Boc_2O , 10% Na_2CO_3 , dioxan;
- g) 1 M LiOH, dioxan;
- 35 h) i) HBTU, DIPEA, DMF; ii) $\text{TFA} \cdot \text{R}_\alpha\text{MePheNH}_2$ (XI).

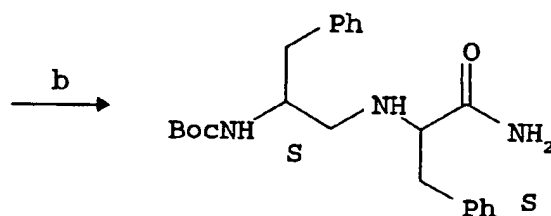
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SCHEME 12

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Example 22

- a) i) DMSO, DCM, oxalyl chloride; ii) Et₃N, DCM;
b) NaCNBH₃, SPhNH₂, MeOH/AcOH (99:1).

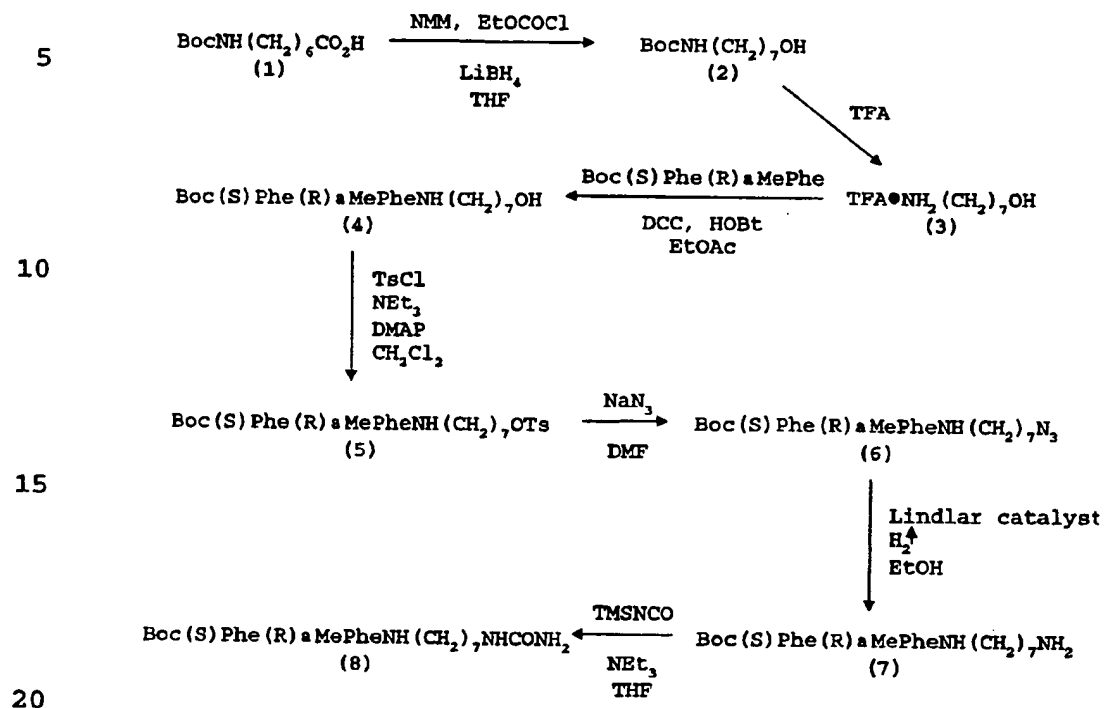
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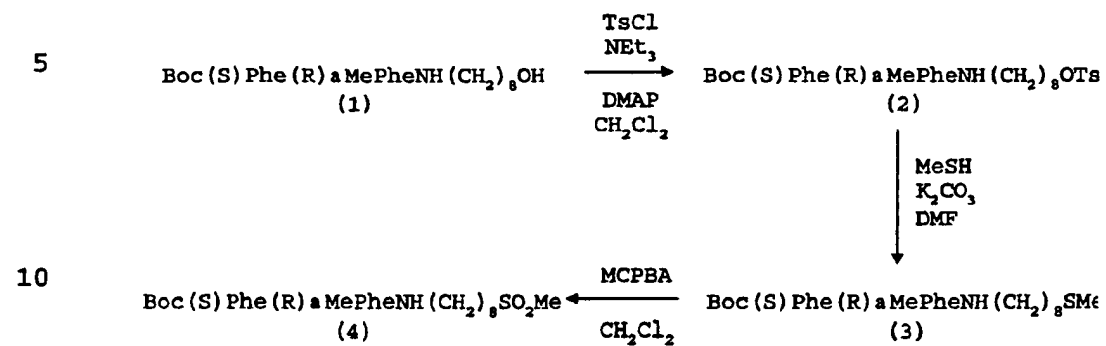
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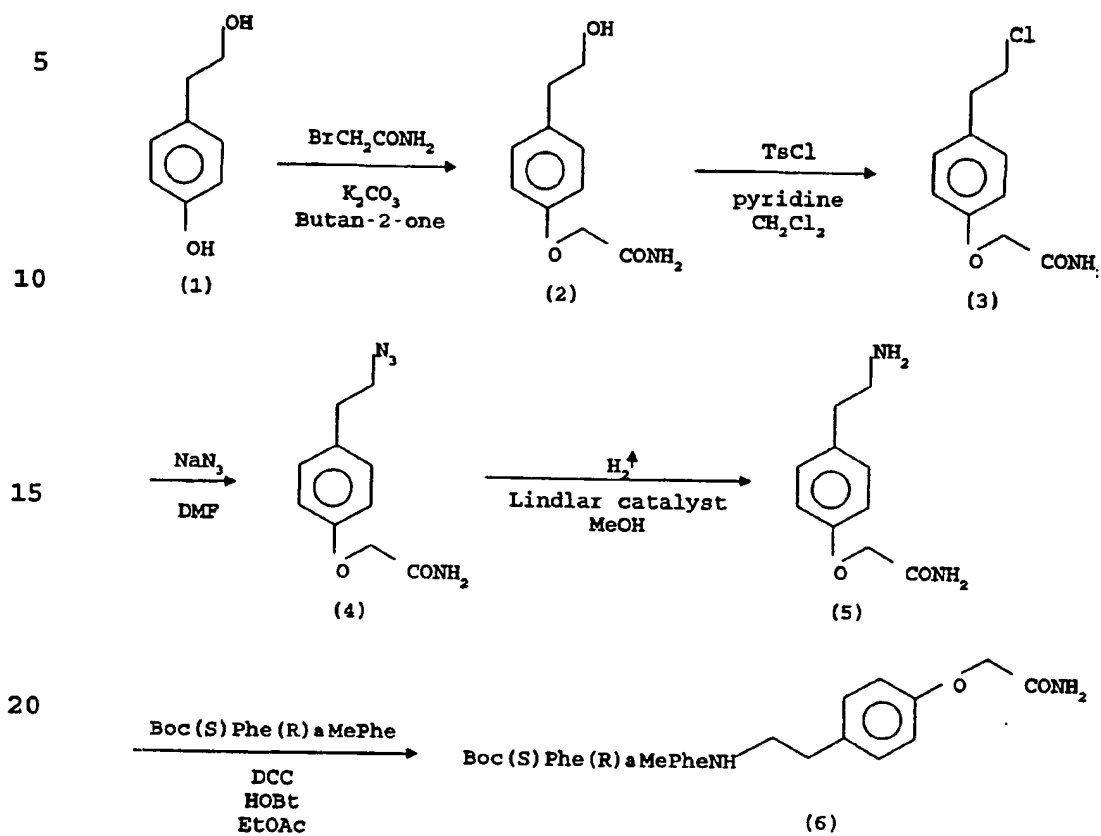
SCHEME 13

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SCHEME 14

- 38 -

SCHEME 15



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The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, intramuscularly, intra-
5 cutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of
10 the present invention can be administered transdermally. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a
15 compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets,
20 pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

25 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in
30 suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% of the active compound. Suitable carriers are magnesium carbonate, magnesium
35 stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium

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carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and

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emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 mg to 200 mg preferably 0.5 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use the highly selective and competitive antagonists of the NK₃ receptor, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 mg to about 500 mg/kg daily. A daily dose range of about 0.01 mg to about 100 mg/kg is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is

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reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

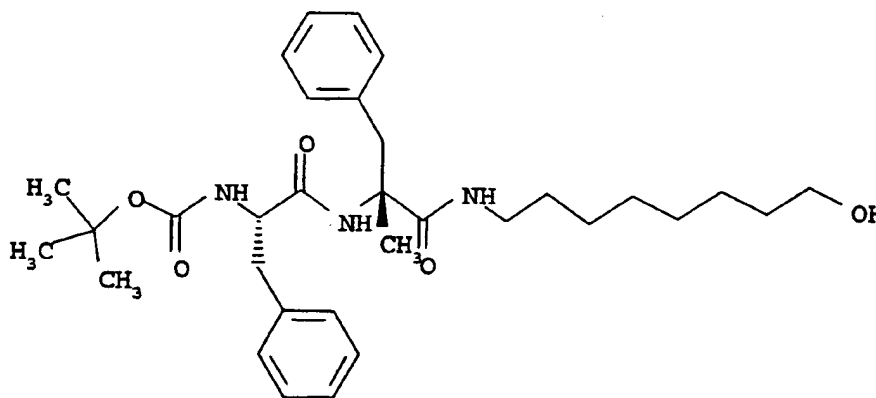
5 The following nonlimiting examples illustrate the methods for preparing the compounds of the invention.

EXAMPLE 1

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-(8-hydroxyoctyl)- α -methyl-

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15



20

Step 1

25

H- α -methyl-[R]-phenylalanine methyl ester

Thionyl chloride (16.2 mL, 225 mmol) was added dropwise over 20 minutes to stirred cooled methanol (120 mL) at -10°C. Following the addition of α -methyl-[R]-phenylalanine (8.08 g, 45 mmol), the mixture was
30 allowed to reach room temperature and stirred for 16 hours. The reaction was then refluxed for 3 hours, cooled, and the methanol removed in vacuo. The residue was taken up in ethyl acetate (300 mL)/saturated aqueous sodium bicarbonate (300 mL). The sodium
35 bicarbonate layer was washed with ethyl acetate and the organic layers combined, washed with water, and dried

-43-

over magnesium sulphate. The ethyl acetate was removed in vacuo to give 6.72 g (78%) of product as an oil;
IR (film): 3376 (NH), 3030, 2951 (CH), 1732 (C = O);
NMR (CDCl₃): 1.41 (3H, s, αCH₃), 2.71-3.23 (2H, m, βCH₂), 3.70 (3H, s, OCH₃), 7.13-7.35 (5H, m, aromatics).

Step 2

10 RoMePheOMe → BocSPheRoMePheOMe

t-Butoxycarbonyl-[S]-phenylalanine-α-methyl-[R]-phenylalaninemethyl ester

15 To a stirred solution of t-butoxycarbonyl-[S]-phenylalanine (8.24 g, 31 mmol) in dimethylformamide (20 mL) was added diisopropylamine (10.74 mL, 62 mmol) and HBTU (11.77 g, 31 mmol). After stirring for 20 minutes at room temperature, α-methyl-[R]-phenylalaninemethyl ester (6 g, 31 mmol) in
20 dimethylformamide was added dropwise over 10 minutes. The reaction was stirred for 5 days. The dimethylformamide removed in vacuo and the residue taken up in ethyl acetate. The ethyl acetate was washed with 2N hydrochloric acid, 10% aqueous sodium
25 bicarbonate, water and brine, dried over magnesium sulphate, and the solvent removed in vacuo. Purification on a flash column using 30% ethyl acetate/hexane increasing to 60% ethyl acetate/hexane gave a white foam, 12.91 g (94%);
30 NMR (CDCl₃): 1.28-1.54 (12H, m, (CH₃)₃C and αCH₃), 2.97-3.37 (4H, m, βCH₂ × 2), 3.72 (3H, s, OCH₃), 4.16-4.30 (1H, m, αCH), 5.00 (1H, m, urethane NH), 6.34 (1H, s, amide), 6.93-7.30 (10H, m, aromatics).

-44-

Step 3

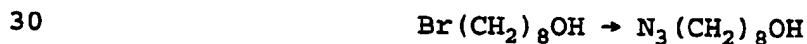
5 t-Butoxycarbonyl-[S]-phenylalanine- α -methyl-
 [R]-phenylalanine

To a stirred solution of t-butoxycarbonyl-[S]-phenylalanine- α -methyl-[R]-phenylalanine methyl ester (12.91 g, 29 mmol) in 1,4-dioxan was added, dropwise over 45 minutes, a 1 M aqueous lithium hydroxide solution (58.5 mL, 58 mmol). The mixture was stirred overnight and the solvents removed in vacuo. The residue was partitioned between ethyl acetate (200 mL) and water (500 mL). The aqueous layer was acidified to pH 3 with 2 M hydrochloric acid (~29 mL) and extracted with ethyl acetate (3 x 200 mL). The organic layers were washed with water, dried over magnesium sulphate, and evaporated to give a white solid, 10.35 g (83%), mp 123-128°C;

15 $[\alpha]_{\text{D}}^{21} = +6.0^{\circ}\text{C}$ (C = 0.68 in MeOH);

20 NMR (CDCl₃): 1.34 (9H, s, (CH₃)₃C), 1.58 (3H, s, α CH₃), 2.91-2.94 (2H, m, β CH₂), 3.24, 3.37 (2H, 2 x d, J = 13.6 Hz, β CH₂), 4.45-4.55 (1H, m, α CH), 5.18-5.28 (1H, m, urethane), 6.70 (1H, s, amide), 7.06-7.29 (10H, m, aromatics) IR (film) 3322 (NH), 2925 (CH), 1709 (urethane, C = O), 1660 (amide I).

25

Step 48-Azido-octan-1-ol

8-Bromo-octan-1-ol (2.61 g, 12.5 mmol) was dissolved in Dmf (30 mL) and sodium azide (0.89 g, 13.75 mmol) was added. The reaction was heated to 90°C and stirred overnight. The solution was then cooled to

35

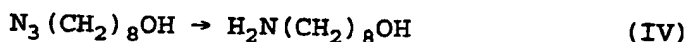
-45-

room temperature and poured onto ice. The aqueous was extracted with DCM (3 x 200 mL) and the combined extracts were washed with brine (2 x 200 mL), then dried over MgSO₄. The solution was filtered and the solvent was removed in vacuo to give a yellow oil, 1.99 g (93% yield);

IR (film): 3355, 2932, 2858, and 2096 cm⁻¹;

NMR (CDCl₃): δ 1.34-1.59 (8H, m, CH₂ x 4), 3.25 (2H, t, J = 7 Hz, CH₂N₃), 3.64 (2H, t, J = 6.6 Hz, CH₂OH).

Step 5



8-amino-octan-1-ol

8-Azido-octan-1-ol (1.99 g, 11.6 mmol) was dissolved in ethanol (25 mL) and Lindlar catalyst (200 mg) was added. The solution was hydrogenated at 50 psi, 30°C for 2 hours. The catalyst was removed by filtration through Kieselguhr and the solvent was removed in vacuo to give a white solid 1.33 g (79% yield), mp 48-53°C;

IR (film): 3346, 2927, 2855, 1610, 1597, and 1485 cm⁻¹;

NMR (CDCl₃): δ 1.32-1.58 (13H, m, CH₂ x 6, OH), 2.68 (2H, t, J = 6.9 Hz, CH₂NH₂), 3.62 (2H, t, J = 6.6 Hz, CH₂OH).

Step 6



Boc-SPheRαMePheNH(CH₂)₈OH

BocSPheRαMePheOH (1.71 g, 4 mmol) was dissolved in DMF (10 mL) and DCC (0.83 g, 4 mmol) added.

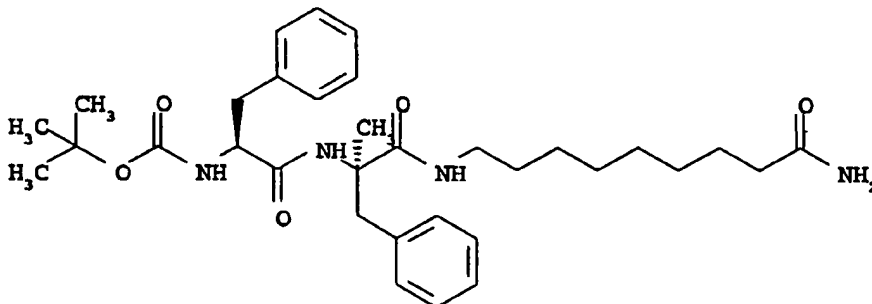
1-Hydroxybenzotriazole (0.54 g, 4 mmol) was added and

-46-

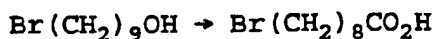
the solution was stirred for 5 minutes. 8-Amino-octan-1-ol (0.64 g, 4.4 mmol) and a catalytic amount of DMAP was added and the reaction was stirred for 24 hours. The precipitate was removed by filtration and the filtrate concentrated in vacuo. The residue was redissolved in EtOAc (100 mL) and washed with dilute HCl (3 x 100 mL), 10% NaHCO₃ (3 x 100 mL), water (3 x 100 mL), and brine (100 mL). The organic was dried over MgSO₄, filtered, and the solvent then removed in vacuo. The product was purified by medium pressure, reverse phase chromatography 0% to 100% MeOH in water over 30 minutes, to give a white solid 1.51 g (68%), mp 43-45°C; $[\alpha]_D^{19.8} = +9.9^\circ\text{C}$ (C = 1.1 in MeOH); IR (film): 3339, 2931, 2856, 1686, 1652, and 1524 cm⁻¹; NMR (CDCl₃): δ 1.29-1.57 (24H, m, BocCH₃ x 3, α CH₃, CH₂ x 6), 2.70-3.45 (6H, m, β CH₂ x 2, CONHCH₂), 3.65 (2H, m, CH₂OH), 4.00 (1H, m, α CH), 4.95 (1H, br.d, urethane NH), 5.85 (1H, s, amide NH), 6.65 (1H, s, amide NH), 6.95-7.34 (10H, m, aromatics); MS (CI): 554 (M⁺), 454, 134; Analysis calculated for C₃₂H₄₇N₃O₅: C, 69.41; H, 8.55; N, 7.59. Found: C, 69.25; H, 8.23; N, 7.52.

EXAMPLE 2

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-(9-amino-9-oxononyl)- α -methyl-



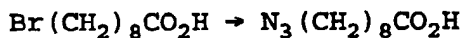
-47-

Step 15 9-Bromo-nonanoic acid

9-Bromo-1-nonanol (4 g, 18 mmol) was placed in a flask, cooled on an ice bath, and concentrated nitric acid (40 mL) was slowly added. The solution was stirred at 0°C for 30 minutes then allowed to warm to room temperature and stirring continued overnight. The solution was poured onto ice and extracted with DCM (3 x 150 mL). The combined extracts were washed with water (3 x 150 mL) and the solvent then removed in vacuo to give an oil 3.82 g (94%);

10 IR (film): 2932, 2857, 1709 cm^{-1} ;

15 NMR (CDCl_3): 1.25-1.48 (8H, m, $\text{CH}_2 \times 4$), 1.62 (2H, m, CH_2), 1.83 (2H, m, CH_2), 2.35 (2H, t, $\text{CH}_2\text{CO}_2\text{H}$), 3.39 (2H, t, CH_2Br).

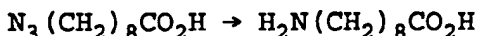
20 Step 29-Azido-nonanoic acid

25 9-Bromo-nonanoic acid (3.82 g, 17 mmol) was dissolved in DMF (30 mL) and sodium azide (1.11 g, 17 mmol) was added. The solution was heated to 80°C and stirred overnight. The reaction was poured onto ice and extracted with DCM (3 x 200 mL). The combined

30 extracts were washed with water (3 x 200 mL), brine (200 mL), and dried over MgSO_4 . The solvent was removed in vacuo to give a clear oil 2.83 g (84% yield);

35 IR (film): 2934, 2858, 2098, and 1706 cm^{-1} .

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Step 35 9-Amino-nonanoic acid

9-Azido-nonanoic acid (2.83 g, 14.2 mmol) was dissolved in ethanol (30 mL) and Lindlar catalyst (300 mg) added. The solution was hydrogenated at 50 psi, 30°C for 4 hours, after which the catalyst was removed by filtration through Kieselguhr, washing with methanol. The solvent was removed in vacuo to give a pale yellow solid, 1.7 g (70%);
IR (film): 2925, 2854, and 1558 cm^{-1} ;
NMR (CD_3OD): δ 1.31-1.45 (8H, m, $\text{CH}_2 \times 4$), 1.55-1.70 (4H, m, $\text{CH}_2 \times 2$), 2.35 (2H, t, $\text{CH}_2\text{CO}_2\text{H}$), 2.88 (2H, t, CH_2NH_2).

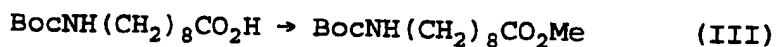
10
15Step 4

9-Amino-nonanoic acid (1 g, 5.8 mmol) was dissolved in 1 M NaOH (6.4 mL) and di-tert-butyldicarbonate (1.4 g, 6.4 mmol) in dioxan (7 mL) was added. Na_2CO_3 (1.83 g, 6.4 mmol) was added and the solution was stirred overnight. The reaction was concentrated in vacuo and the residue was redissolved in water. The aqueous was washed with ether, the pH was then adjusted to four with dilute HCl. The aqueous was then extracted with EtOAc (3 \times 200 mL). The combined extracts were washed with water (3 \times 200 mL), brine (200 mL), and dried over MgSO_4 . After filtration, the solvent was removed in vacuo to give a yellow oil 1.14 g (72%);
IR (film): 3339, 2932, 2858, and 1714 cm^{-1} ;

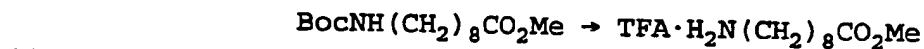
25
30
35

-49-

NMR (CDCl₃): δ 1.20-1.65 (21H, m, BocCH₃ \times 3, CH₂ \times 6), 2.33 (2H, m, CH₂CO₂H), 3.11 (2H, m, NHCH₂), 4.60 (1H, s, NH).

5 Step 5

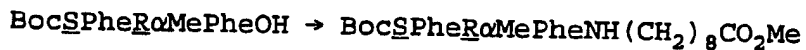
10 BocNH(CH₂)₈CO₂H (1.02 g, 3.7 mmol) was dissolved in methanol (20 mL) and DCC (0.75 g, 3.7 mmol) added. A catalytic amount of DMAP was added and the reaction was stirred for 48 hours. The precipitate was removed by filtration and the solvent was removed in vacuo to give an oil 1.33 g. The crude product was used without
15 purification.

Step 6

BocNH(CH₂)₈CO₂Me (1.33 g, 4.6 mmol) was dissolved in a 50:50 mixture of DCM/TFA (20 mL). The solution was stirred for 1 hour after which the solvent was removed in vacuo. A partial purification was carried
25 out using medium pressure reverse phase chromatography 0-100% MeOH in H₂O, yield 0.78 g (56%);
IR (film): 2934, 2858, 1736, and 1682 cm⁻¹.

Step 7

30



BocSPheR α MePheOH (I, prepared Example 1, Step 3) (0.85 g, 2 mmol) was dissolved in DMF (10 mL) and HBTU (0.76 g, 2 mmol) and DIPEA (348 μ L, 2 mmol) were added.
35 The solution was stirred for 10 minutes, after which

-50-

the trifluoroacetate salt of $\text{H}_2\text{N}(\text{CH}_2)_8\text{CO}_2\text{Me}$ (0.78 g, 2.5 mmol) was added. DIPEA (790 μL , 4.5 mmol) was added and the reaction was stirred overnight. The solution was concentrated in vacuo and the residue was redissolved in EtOAc (100 mL). The organic was washed with dilute HCl (3 \times 100 mL), saturated NaHCO_3 (3 \times 100 mL), water (3 \times 100 mL), and brine (100 mL) then dried over MgSO_4 . After filtration the solvent was removed in vacuo and the residue was purified by chromatography. Sorbsil 60, 2% MeOH/DCM. A white solid was isolated 350 mg, which was shown to be a mixture of the required product and the BocSPheRoMePheNH(CH₂)₇CO₂Me analog;

IR (film): 3343, 2978, 2932, 2857, 1735, 1689, 1650, and 1520 cm^{-1} ;

NMR (CDCl_3): δ 1.27-1.62 (24H, m, BocCH₃ \times 3, αCH_3 , CH₂ \times 6), 2.29 (2H, t, $\underline{\text{CH}_2\text{CO}_2\text{R}}$), 2.68-3.43 (6H, m, CONHCH₂, βCH_2 \times 2), 3.65 (3H, s, $\underline{\text{OCH}_3}$), 4.01 (1H, m, αCH), 5.00 (1H, s, urethane NH), 5.95 (1H, s, NH), 6.70 (1H, s, NH), 6.96-7.36 (10H, m, aromatics);

HPLC: 40-100% B over 20 minutes, A = H₂O, B = CH₃CN, 0.1% TFA, R_t = 16.8 and 17.8 minutes.

Step 8

BocSPheRoMePheNH(CH₂)₈CO₂Me \rightarrow BocSPheRoMePheNH(CH₂)₈CO₂H

The methyl esters (Step 7) (370 mg, 0.6 mmol) were dissolved in dioxan (3.6 mL) and 1 M LiOH (1.2 mL), the solution was stirred for 2 hours. The solvent was removed in vacuo and the residue was redissolved in water, then washed with ether. The pH of the aqueous was adjusted to four with dilute HCl and then extracted with DCM (3 \times 100 mL). The combined extracts were washed with water (3 \times 100 mL) and brine (100 mL), dried over MgSO_4 , filtered, and the solvent removed

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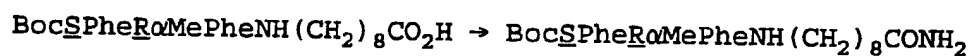
in vacuo. The crude product was purified by medium pressure reverse phase chromatography 80% MeOH in H₂O to give a white solid 290 mg, again a mixture of the C₈ and C₉ chains;

5 NMR (CDCl₃): δ 1.22-1.70 (24H, m, BocCH₃ \times 3, α CH₃, CH₂ \times 6), 2.35 (2H, t, CH₂CO₂H), 2.75-3.48 (6H, m, β CH₂ \times 2, CONHCH₂), 4.02-4.15 (1H, m, α CH), 4.95, 5.08 (1H, 2 \times br s, urethane NH), 5.90, 5.95 (1H, 2 \times s, amide NH's), 6.60 (1H, br s, amide NH), 6.95-7.38 (10H, m, aromatics);

10 HPLC: 40-100% B over 20 minutes, A = H₂O, B = CH₃CN, 0.1% TFA, R_t = 13.6 and 14.5 minutes.

Step 9

15



The mixture of acids (Step 8) (290 mg, 0.5 mmol) was dissolved in DCM (3 mL) and DCC (103 mg, 0.5 mmol) followed by pentafluorophenol (92 mg, 0.5 mmol) added. The reaction was stirred overnight, then the precipitate removed by filtration. The solvent was removed in vacuo and the ester redissolved in DCM (3 mL). Ammonia was bubbled through the solution for 5 minutes and the solvent then removed in vacuo, to give a crude product 210 mg. Purification was carried out by reverse phase HPLC 57-67% B over 40 minutes, A = H₂O, B = CH₃CN, 0.1% TFA to give a white solid 93 mg (32%), mp 45-47°C;

20 IR (film): 3340, 2932, 1698, 1656, and 1528 cm⁻¹;

MS (FAB) 603 (M+Na), 581 (M+H), 481, 334, 173, 134;

25 NMR (CDCl₃): δ 1.29-1.48 (22H, m, BocCH₃ \times 3, α CH₃, CH₂ \times 5), 1.65 (2H, m, CH₂), 2.26 (2H, t, CH₂CONH₂), 2.70-3.45 (6H, m, β CH₂ \times 2, CONHCH₂), 4.0 (1H, m, α CH),

30 4.95 (1H, m, urethane NH), 5.90 (1H, s, amide NH),

35

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6.05, 6.35 (2H, 2 x s, CONH₂), 6.75 (1H, s, amide NH),
6.96-7.37 (10H, m, aromatics);

HPLC: 40-100% B over 20 minutes, A = H₂O, B = CH₃CN,
0.1% TFA, R_t = 12.0 minutes;

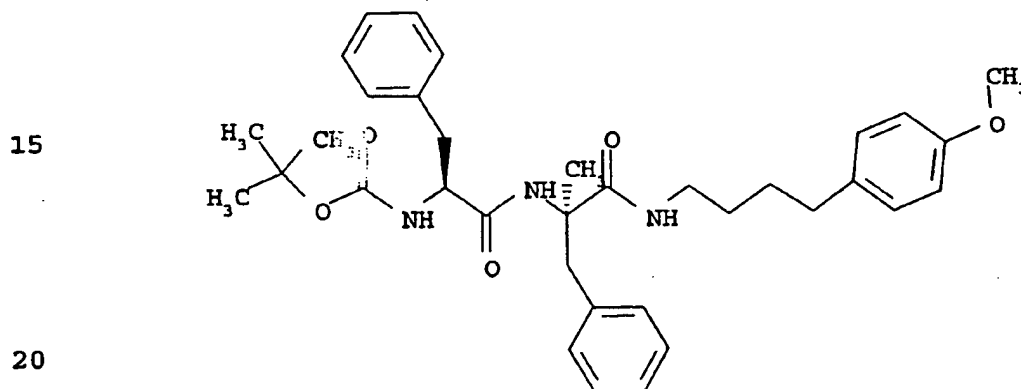
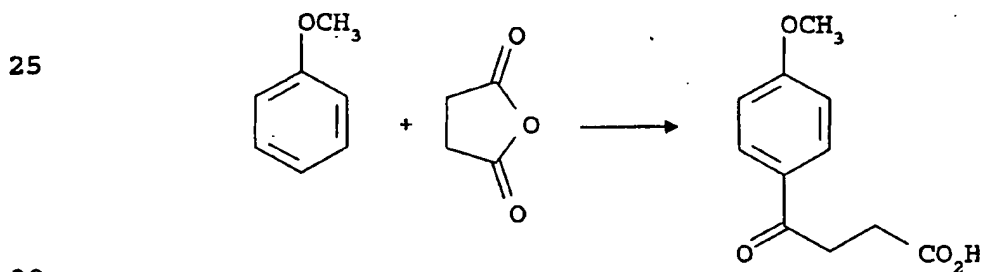
5 Analysis calculated for C₃₃H₄₈N₄O₅·0.7 TFA:

C, 62.54; H, 7.43; N, 8.48.

Found: C, 62.24; H, 7.50; N, 8.48.

EXAMPLE 3

10 D-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-[4-(4-methoxyphenyl)butyl-α-methyl-

Step 1

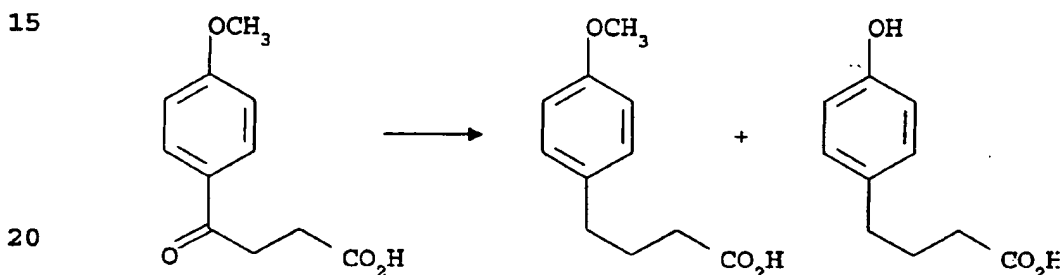
35 Anhydrous aluminium chloride (8.00 g, 60 mmol) and
succinic anhydride (3.00 g, 30 mmol) in nitroethane
(80 mL) were stirred under N₂ at 0°C for 1 hour.
Anisole (3.26 mL, 30 mmol) was added dropwise over
5 minutes. The resulting mixture was stirred below

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15°C for 6 hours and then at room temperature for 15 hours.

The deep red solution was poured onto 200 mL crushed ice containing 100 mL 2 M HCl and 10 mL concentrated HCl, and stirred vigorously for 1.5 hours. Extraction with DCM, drying (MgSO₄), and purification by flash chromatography using ethyl acetate:hexane (1:1) gave a white solid (3.48 g, 56%);
M/e (CI): 191 (100%), 209 (M+1);
NMR (CDCl₃): δ 2.80 (2H, t, -CH₂-), 3.26 (2H, t, -CH₂-), 3.87 (3H, s, -OCH₃), 6.93 (2H, d, Ar), 7.95 (2H, d, Ar).

Step 2



Hydrazine monohydrate (1.61 mL, 33.2 mmol), the ketone (3.46 g, 16.6 mmol) and potassium hydroxide pellets (3.77 g, 66.4 mmol) were heated under reflux in diethylene glycol (20 mL) for 1.5 hours. The temperature was then increased to 180°C for 2 hours during which time the hydrazine and water distilled over. On cooling, an additional 1.61 mL hydrazine hydrate was added and the process was repeated.

On completion, 10% citric acid solution (130 mL) was added and the mixture was extracted with ether. The ether layer was washed with water and dried (MgSO₄) and further purified by column chromatography in ether:hexane (2:3) yielding a white solid (2.30 g, 71%);
IR (film): 1707 and 2936 cm⁻¹;

-54-

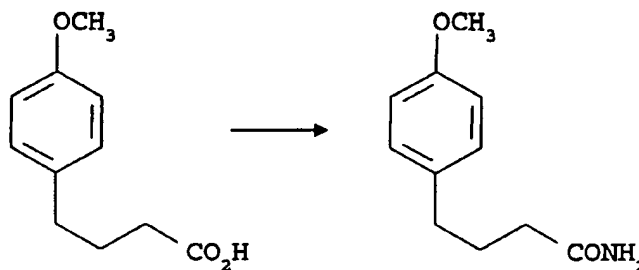
M/e (CI): 177 (100%), 194 (M);

NMR (CDCl₃): δ 1.93 (2H, quint, -CH₂-), 2.35 (2H, t, -CH₂-), 2.61 (2H, t, -CH₂-), 3.78 (3H, s, -OCH₃), 6.82 (2H, d, Ar), 7.08 (2H, d, Ar);

5

Step 3

10



15

4-(4-Methoxyphenyl)butanoic acid (1.18 g, 6.07 mmol) and triethylamine (0.847 mL, 6.07 mmol) were dissolved in DCM (40 mL) at 0°C. Ethyl chloroformate (0.581 mL, 6.07 mmol) was added dropwise and the resulting solution was stirred at 0°C for 45 minutes. DMF (10 mL) was added and a slow stream of ammonia gas was bubbled through the solution for 45 minutes. The resulting mixture was stirred for 18 hours at room temperature.

20

On removal of the solvents, the residue was taken up in ethyl acetate and washed with water, 2 M HCl, and 10% Na₂CO₃ solution. Drying (MgSO₄) and evaporation gave an off-white solid (0.86 g, 73%);

25

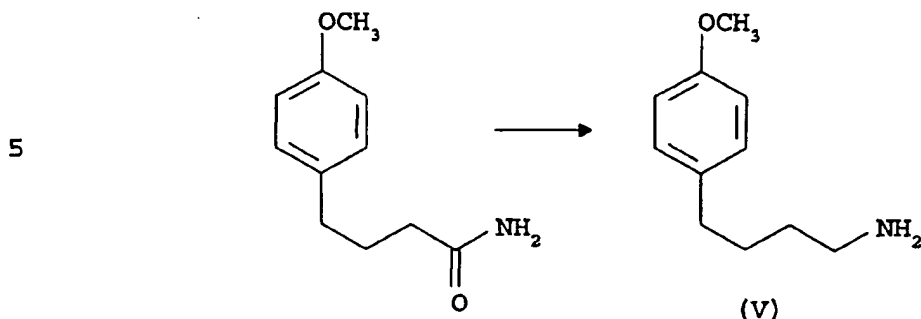
IR (film): 3363, 1659, and 1629 cm⁻¹;

M/e (CI): 194 (M+1);

30

NMR (DMSO-d₆): δ 1.72 (2H, quint, -CH₂-), 2.03 (2H, t, -CH₂-), 2.48-2.51 (2H, obs by DMSO, -CH₂-), 3.71 (3H, s, -OCH₃), 6.71 (1/2 \times 2H, bs), 7.24 (1/2 \times 2H, bs, -CONH₂), 6.80-7.12 (4H, m, Ar).

-55-

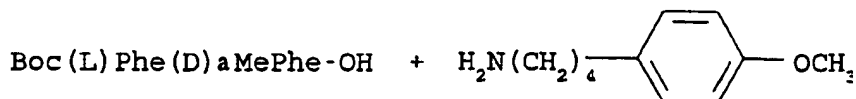
Step 4

10 2 M BMS in THF (4.8 mL, 9.66 mmol) was added
dropwise over 15 minutes to a solution of
4-(4-methoxyphenyl)butanamide (0.80 g, 4.14 mmol) in
THF (30 mL) at room temperature under N₂. The
resulting mixture was stirred at room temperature for
15 1.5 hours and heated at reflux for 5 hours. On cooling
to 0°C, methanol (2 mL) was added dropwise, the
temperature was not allowed to rise above 15°C. The
mixture was allowed to stir for 2 days. HCl(g) was
bubbled through the solution for ~3 minutes and the
20 resulting solution was heated at reflux for 1 hour.

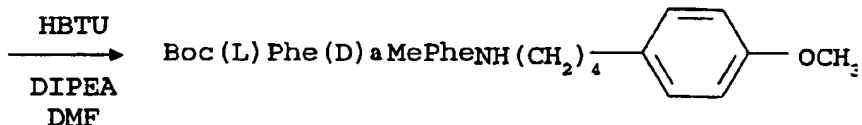
On cooling, the mixture was evaporated to dryness
and the residue was partitioned between water and ethyl
acetate. The aqueous layer was adjusted to pH 10 with
NaOH and extracted with ethyl acetate. Drying (MgSO₄)
25 and further purification by flash chromatography using
10% MeOH/DCM gave a white solid (0.230 g, 31%);
NMR (DMSO-d₆): 1.28-1.44 (2H, m, -CH₂-), 1.43-1.62
(2H, m, -CH₂-), 2.44-2.60 (4H, obs, by DMSO,
2 x -CH₂-), 3.71 (3H, s, -OCH₃), 6.80-7.11 (4H, m, Ar).

30

-56-

Step 5

5



10

Boc(L)Phe(D) α MePhe-OH (I, from Example 1, Step 3) (0.247 g, 0.58 mmol), HBTU (0.220 g, 0.58 mmol), and diisopropylethylamine (0.280 mL, 1.16 mmol) were stirred together in DMF (5 mL) at room temperature for 20 minutes. 4-(4-Methoxyphenyl)butyl amine (0.104 g, 0.58 mmol) in DMF (2 mL) was then added. The mixture was stirred for 24 hours at room temperature.

15

On removal of the DMF, the residue was taken up in ethyl acetate and washed with 2 M HCl, 1 M NaOH, and water. Drying (MgSO₄) and further purification by

20

flash chromatography using 2.5% MeOH/DCM gave a white solid (0.223 g, 65%), mp 44-48°C;
 $[\alpha]_D^{26.4} = +4.26$ (C = 1.01, MeOH);
 IR (film): 3334, 2932, 1683, and 1652 cm⁻¹;
 M/e (CI): 588 (M+1), 134 (100%);

25

NMR (DMSO-d₆): δ 1.10-1.50 (16H, m, Boc, α Me, -CH₂- x 2), 2.40-2.50 (2H, obs by DMSO, -CH₂-), 2.60-3.20 (6H, m, 4 x β -CH₂-, -CH₂-), 3.65 (3H, s, -OCH₃), 4.12 (1H, m, α H), 6.75-7.25 (15H, m, Ar, -CONH-), 7.51 (1H, t, -CONH-CH₂-), 7.71 (1H, s, -CONH-);

30

Analysis calculated for C₃₅H₄₅N₃O₅:

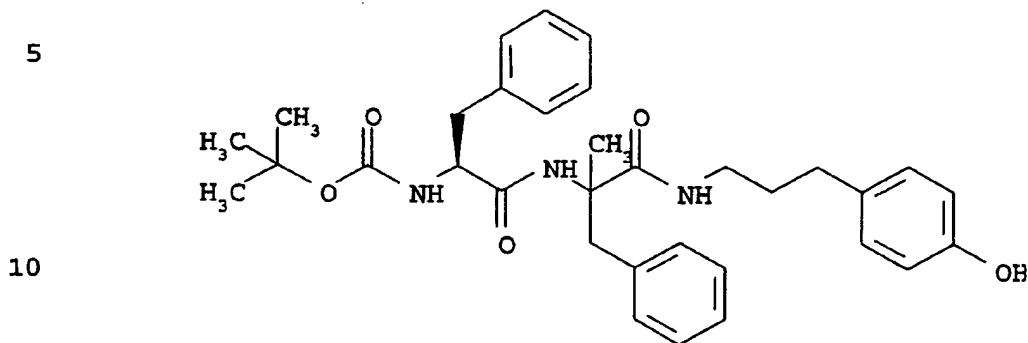
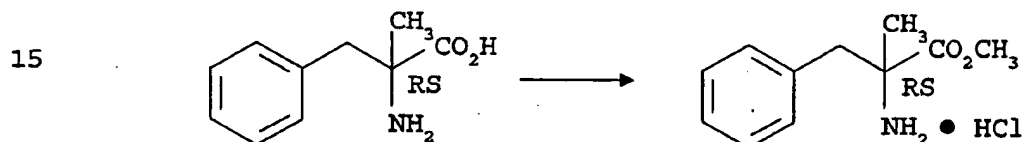
C, 71.52; H, 7.72; N, 7.15.

Found: C, 71.19; H, 7.82; N, 7.09.

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EXAMPLE 4

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-[3-(4-hydroxyphenyl)propyl]- α -methyl-

Step 1

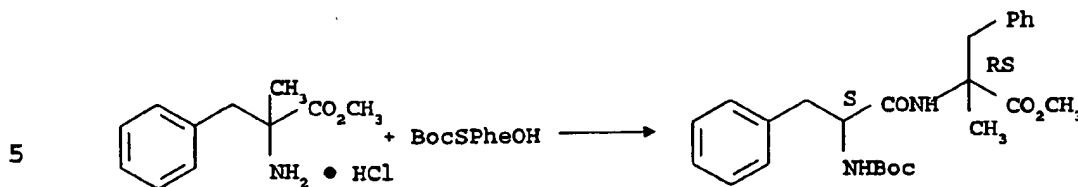
Thionyl chloride (10.1 mL, 140 mmol) was added dropwise over 5 minutes to MeOH (100 mL) stirred in a cooling bath at -10°C. RS- α -MePheOH (5.0 g, 27.9 mmol) was added at -10°C and the solution stirred overnight with slow rewarming to room temperature. The solution was heated at reflux for 1 hour, allowed to cool, and the solvent removed in vacuo to give the product as an off-white amorphous solid (6.49 g, 100%);

25

NMR (DMSO-*d*₆): δ 1.53 (3H, s, CH₃), 3.13 (1H, d, J = 13.7 Hz, PhCHH), 3.22 (1H, d, J = 13.7 Hz, PhCHH), 3.71 (3H, s, COOCH₃), 7.16-7.36 (5H, m, C₆H₅), 8.80 (3H, b, N⁺H₃).

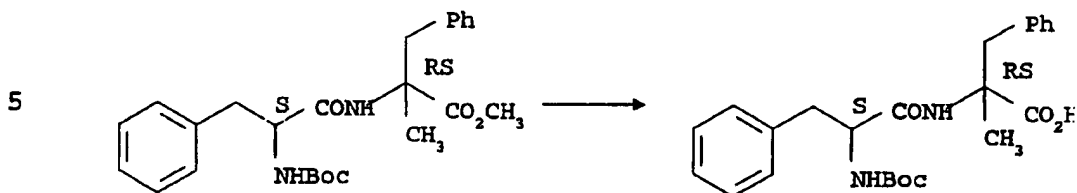
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Step 2

N,N'-dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) was added to a stirred solution of N-tert-butyloxy-carbonyl-S-phenylalanine (2.65 g, 10 mmol) and
 10 1-hydroxybenzotriazole monohydrate (1.91 g, 12.5 mmol) in EtOAc (100 mL). The mixture was stirred at room temperature for 2 hours and the N,N'-dicyclohexylurea filtered off. Et₃N (1.53 mL, 11 mmol) was added followed by a solution of the amino ester hydrochloride
 15 (2.30 g, 10 mmol) in EtOAc (25 mL) added dropwise over 10 minutes and the mixture stirred at room temperature for 18 hours. The solution was washed with 5% citric acid solution (2 × 25 mL), saturated NaHCO₃ solution (2 × 25 mL), 5% citric acid solution (25 mL), and once
 20 with brine (25 mL). The EtOAc solution was dried over MgSO₄, filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 67% n-hexane/33% EtOAc as eluant giving the product as a white solid (1.99 g, 45%), mp 40-46°C;
 25 IR (film): 3332, 1741, and 1664 cm⁻¹;
 NMR (CDCl₃): δ 1.37, 1.40 (9H, 2s, C(CH₃)₃), 1.54 (3H, s, CH₃), 2.93-3.16 (3H, m, PhCH₂, PhCHH), 3.32-3.44 (1H, m, PhCHH), 3.71, 3.72 (3H, 2s, CO₂CH₃), 4.20-4.35 (1H, m, CH₂CH), 5.00 (1H, b, NHCOO), 6.38 (1H, d, J = 9.0 Hz, CONH), 6.88-6.96 (2H, m, Ph), 7.15-7.32 (8H, m, Ph);
 30 Analysis calculated for C₂₅H₃₂N₂O₅·0.25H₂O.

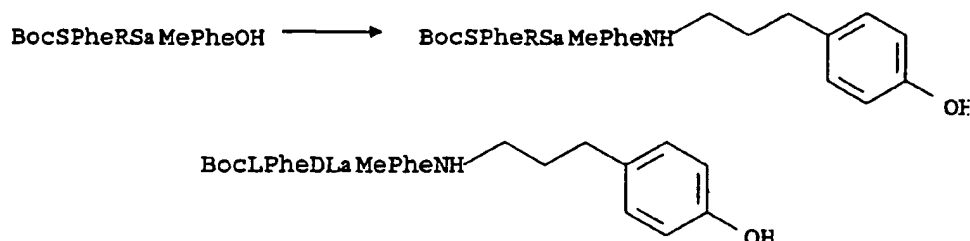
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Step 3

(II)
 1N LiOH solution (4.34 mL, 4.34 mmol) was added
 10 dropwise over 30 minutes to a stirred solution of the
 methylester (1.74 g, 3.95 mmol) in THF:H₂O (50 mL,
 4:1 mixture) cooled to 0°C. The mixture was stirred
 with slow rewarming to room temperature for 4 days and
 then the THF removed in vacuo. The residue was diluted
 15 with water (25 mL) and extracted once with EtOAc
 (25 mL). The remaining aqueous solution was acidified
 with 5% citric acid solution and the product extracted
 into EtOAc (2 × 25 mL). The combined EtOAc extracts
 were dried over MgSO₄, filtered, and the solvent
 20 removed in vacuo giving the product as a white solid
 (1.04 g, 62%), mp 106.8-107.7°C;
 IR (film): 1719 and 1662 cm⁻¹;
 NMR (DMSO-d₆): δ 1.20-1.36 (12H, m, C(CH₃)₃, CH₃),
 2.66-2.74 (1H, m, PhCH₂), 2.93-3.35 (3H, m, PhCH₂,
 25 PhCH₂), 4.10-4.22 (1H, m, CH₂CH), 6.93-7.01 (1H, m,
 NHCOO), 7.07-7.27 (10H, m, 2C₆H₅), 7.63, 7.90 (1H, 2s,
 CONH), 12.65 (1H, b, COOH);
 Analysis calculated for C₂₄H₃₀N₂O₅·0.25H₂O:

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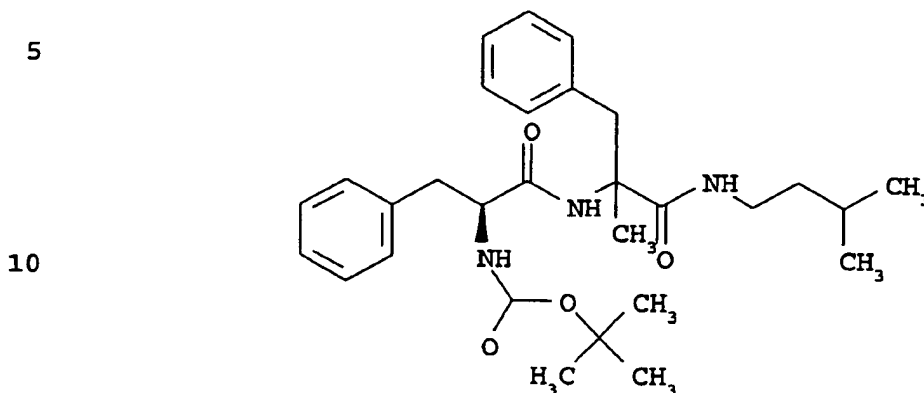
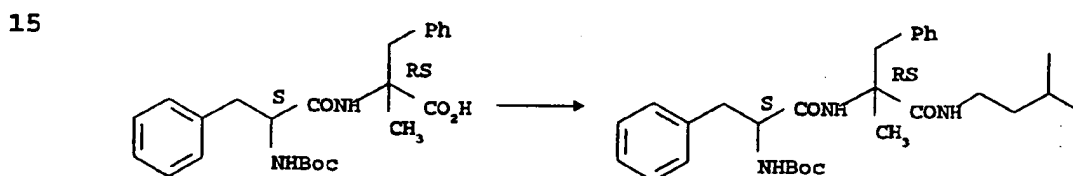
Step 4

10 To a stirred solution of Boc-L-Phe-DL-αMePhe (II)
 (0.20 g, 0.47 mmol) in dimethylformamide (5 mL) was
 added HBTU (0.18 g, 0.47 mmol), diisopropylethylamine
 (0.12 g, 0.94 mmol), and 3-(4-hydroxyphenyl)propylamine
 (0.07 g, 0.47 mmol). The reaction was stirred at room
 15 temperature for 20 hours and then concentrated under
 reduced pressure. The residue was taken up in ethyl
 acetate and the organic layer washed with 0.1N
 hydrochloric acid, dried over magnesium sulphate, and
 the solvent removed in vacuo. Purification by column
 20 chromatography gave the product as a white amorphous
 solid, 0.04 g (15%), mp 57-60°C;
 IR (film): 3338 (NH), 2933 (CH), 1689 (urethane,
 C = O), 1652 (amide I), 1516 (amide II);
 NMR (CDCl₃): 1.30, 1.35 (9H, 2 × s, (CH₃)₃C), 1.47,
 25 1.57 (3H, 2 × s, αCH₃), 1.69-1.79 (2H, m, CH₂CH₂CH₂),
 2.47-2.54 (2H, m, CH₂-Ph), 2.69-3.38 (6H, m, βCH₂ × 2,
 NHCH₂), 3.97-4.15 (1H, m, αCH), 4.90, 5.04 (1H, 2 × d,
 J = 5.5 and 5.7 Hz, urethane NH), 5.82, 6.18 (1H,
 2 × s, amide), 6.55-6.70 (1H, m, amide), 6.71-6.77 (2H,
 30 m, aromatics), 6.91-6.97 (4H, m, aromatics), 7.13-7.35
 (8H, m, aromatics);
 Analysis calculated for C₃₃H₄₁N₃O₅·0.25H₂O.

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EXAMPLE 5

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl- α -methyl-N-3-methylbutyl-

Step 1

20 N,N'-dicyclohexylcarbodiimide (0.129 g, 0.63 mmol) was added to a stirred solution of the acid (II, from Example 4, Step 3) (0.242 g, 0.57 mmol) and 1-hydroxybenzotriazole monohydrate (0.105 g, 0.68 mmol) in EtOAc (25 mL). The mixture was stirred at room

25 temperature for 2 hours and the N,N'-dicyclohexylurea filtered off. Isoamylamine (0.075 g, 0.86 mmol) in EtOAc (2 mL) was added dropwise over 2 minutes and the mixture stirred at room temperature for 18 hours. The solution was washed with 5% citric acid solution

30 (2 x 25 mL), saturated NaHCO₃ (2 x 25 mL), 5% citric acid (25 mL), and once with brine (25 mL). The EtOAc solution was dried over MgSO₄, filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 67% n-hexane 33% EtOAc and then 50% n-hexane/50% EtOAc as eluant to give the

35 product as a white solid (0.123 g, 44%); mp 80-93°C;

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IR (film): 3332, 2958, 1689, and 1651 cm^{-1} ;

NMR (CDCl_3): δ 0.89 (6H, d, $J = 6.6$ Hz, $(\text{CH}_3)_2\text{CH}$),
 1.33, 1.37 (9H, 2s, $\text{NHCOOC}(\text{CH}_3)_3$), 1.25-1.44 (2H, m,
 $\text{CCH}_2\text{CH}(\text{CH}_3)_2$), 1.49, 1.58 (3H, 2s, CH_3), 1.52-1.64 (1H,
 5 m, $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$), 2.77-3.44 (6H, m, 3CH_2), 4.00-4.13
 (1H, m, CH_2CHNCO), 4.87-4.98 (1H, m, $\text{NHCOOC}(\text{CH}_3)_3$),
 5.92, 6.26 (1H, 2s, CONH), 6.54, 6.67 (1H, 2s, CONH),
 6.96-6.98 (2H, m, Ph), 7.16-7.36 (8H, m, Ph);

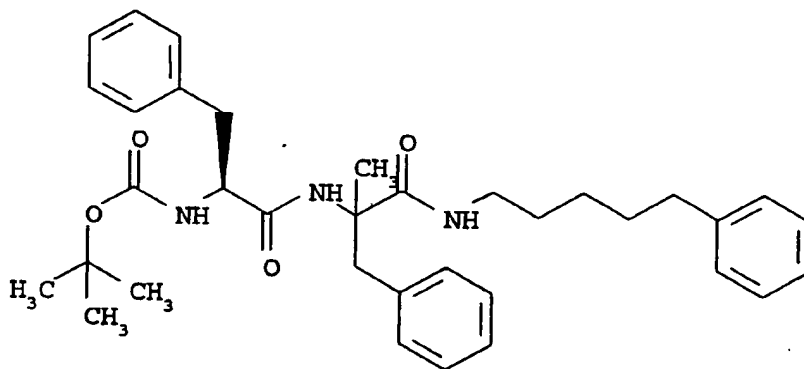
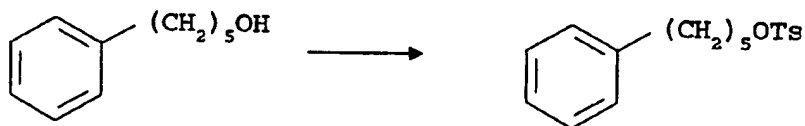
Analysis calculated for $\text{C}_{29}\text{H}_{41}\text{N}_3\text{O}_4$:

C, 70.27; H, 8.34; N, 8.48.

Found: C, 70.37; H, 8.56; N, 8.19.

EXAMPLE 6

D,L-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
 15 L-phenylalanyl- α -methyl-N-(5-phenylpentyl)-

Step 1

Triethylamine (0.354 g, 3.50 mmol) was added to a
 stirred solution of the alcohol (0.500 g, 3.04 mmol)
 and p-toluene sulfonyl chloride (0.608 g, 3.19 mmol) in
 35 CH_2Cl_2 (5 mL). The mixture was stirred overnight at
 room temperature and then washed with 0.1 M HCl

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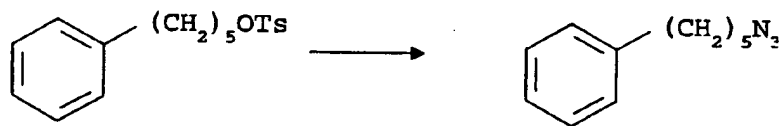
solution and saturated NaHCO_3 solution. The CH_2Cl_2 layer was dried (MgSO_4), filtered, and the solvent removed in vacuo. Purification of the residue by chromatography on silica using 25% EtOAc/75% n-hexane as eluant gave the product as a colorless gum (0.538 g, 56%);

IR (film): 2993, 2859, 1359, and 1176 cm^{-1} ;

NMR (CDCl_3): δ 1.30 (2H, m, CH_2), 1.65 (4H, m, CH_2CH_2), 2.45 (3H, s, CH_3), 2.55 (2H, t, $J = 7.0\text{ Hz}$, CH_2CH_2), 4.05 (2H, t, $J = 7.0\text{ Hz}$, CH_2CH_2), 7.10-7.40 (7H, m, C_6H_5 , tosyl), 7.77 (2H, s, $J = 7.0\text{ Hz}$, tosyl).

Step 2

15



Sodium azide (0.090 g, 1.38 mmol) was added to a solution of the tosylate (0.420 g, 1.32 mmol) in DMF (5.0 mL) and the mixture stirred overnight at room temperature. The mixture was poured into water (25 mL), extracted into Et_2O ($2 \times 25\text{ mL}$) the combined Et_2O extracts dried over MgSO_4 , filtered, and the solvent removed in vacuo. This gave the product as a colorless oil (0.229 g, 92%);

IR (film): 3027, 2936, 2859, 2095, and 1495 cm^{-1} ;

NMR (CDCl_3): δ 1.45 (2H, m, CH_2), 1.60 (4H, m, CH_2CH_2), 2.62 (2H, t, $J = 8.0\text{ Hz}$, CH_2CH_2), 3.25 (2H, t, $J = 8.0\text{ Hz}$, CH_2CH_2), 7.15 (3H, m, Ph), 7.25 (2H, m, Ph).

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Step 3

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(VI)

10 A solution of the azide (0.220 g, 1.16 mmol) in 95% EtOAc (70 mL) was hydrogenated overnight at room temperature over Lindlar catalyst (0.110 g) at 30 psi of H₂. The catalyst was filtered and the solvent removed in vacuo to give the crude product as a syrup which was used without purification in Step 4.

15 Step 4

20 N,N'-dicyclohexylcarbodiimide (0.073 g, 0.35 mmol) was added to a stirred solution of the acid (II, prepared, Example 4, Step 3) (0.150 g, 0.35 mmol) and 1-hydroxybenzotriazole monohydrate (0.054 g, 0.35 mmol) in EtOAc (7 mL). The mixture was stirred at room temperature for 2 hours and the N,N'-dicyclohexylurea
 25 filtered off. The amine (0.057 g, 0.35 mmol) was added and the reaction mixture stirred overnight at room temperature. The solvent was removed in vacuo and the residue purified by chromatography on silica using 40% EtOAc/60% n-hexane as eluant to give the product as a
 30 white solid (0.165 g, 83%), mp 85-90°C;
 IR (film): 3326, 2932, 1687, 1665, 1650, 1497, and 1454 cm⁻¹;
 NMR (CDCl₃): δ 1.32, 1.36 (9H, 2s, C(CH₃)₃), 1.50-1.65 (9H, m, CH₃, 3 CH₂), 2.59 (2H, t, J = 7.0 Hz, CH₂CH₂Ph), 2.80-3.40 (6H, m, 3CH₂), 4.05 (1H, m, CH₂CH), 4.80, 4.90 (1H, 2 brs, CHNHCOO),

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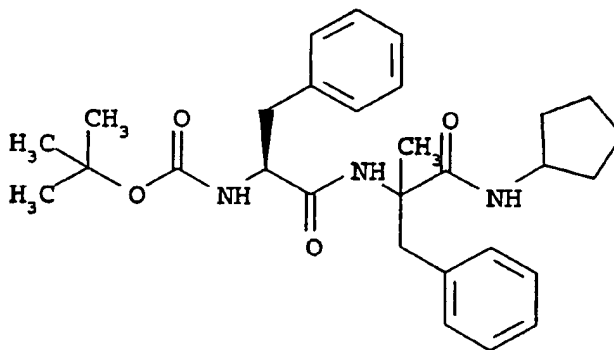
5.85, 6.20 (1H, 2 brs, CONH), 6.50, 6.65 (1H, 2 brs, CONH), 6.95 (2H, brs, Ph), 7.10-7.40 (13H, m, Phs);
Analysis calculated for $C_{35}H_{45}N_3O_4$.

5

EXAMPLE 7

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-cyclopentyl- α -methyl-

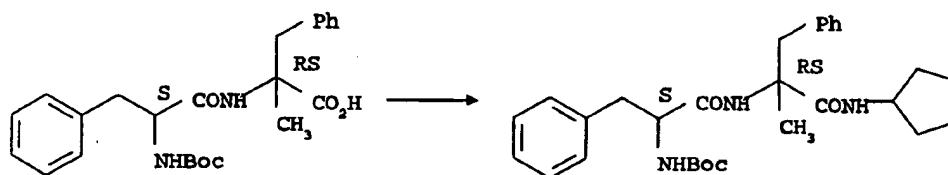
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Step 4

20



25

N,N'-dicyclohexylcarbodiimide (0.107 g, 0.52 mmol) was added to a stirred solution of the acid (II, prepared, Example 4, Step 3) (0.200 g, 0.47 mmol) and 1-hydroxybenzotriazole monohydrate (0.086 g, 0.56 mmol) in EtOAc (20 mL). The mixture was stirred at room temperature for 2 hours and the N,N'-dicyclohexylurea filtered off. Cyclopentylamine (0.060 g, 0.71 mmol) in EtOAc (2 mL) was added dropwise over 2 minutes and the mixture stirred at room temperature for 72 hours. The solution was washed with 5% citric acid solution (2 x 25 mL), saturated NaHCO_3 (2 x 25 mL), 5% citric

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acid (25 mL), and once with brine (25 mL). The EtOAc solution was dried over MgSO_4 , filtered, and the solvent removed in vacuo. The residue was purified by chromatography on silica using 67% n-hexane/33% EtOAc as eluant giving the product as a white solid (0.208 g, 90%), mp 148-155°C;

IR (film): 3329, 2935, 1691, and 1644 cm^{-1} ;

NMR (CDCl_3): δ 1.33, 1.37 (9H, 2s, $\text{NHCOOC}(\text{CH}_3)_3$),

1.46, 1.57 (3H, 2s, CH_3), 1.50-1.70 (6H, m,

cyclopentyl), 1.88-1.99 (2H, m, cyclopentyl), 2.79-3.47

(4H, m, $2\text{CH}_2\text{Ph}$), 4.03-4.20 (2H, m, $2\text{CH}_2\text{CHN}$), 4.81-4.86

(1H, m, $\text{NHCOOC}(\text{CH}_3)_3$), 6.01, 6.32 (1H, 2 bs, CONH),

6.44, 6.58 (1H, 2 bs, CONH), 6.95-7.02 (2H, m, Ph),

7.16-7.36 (8H, m, Ph);

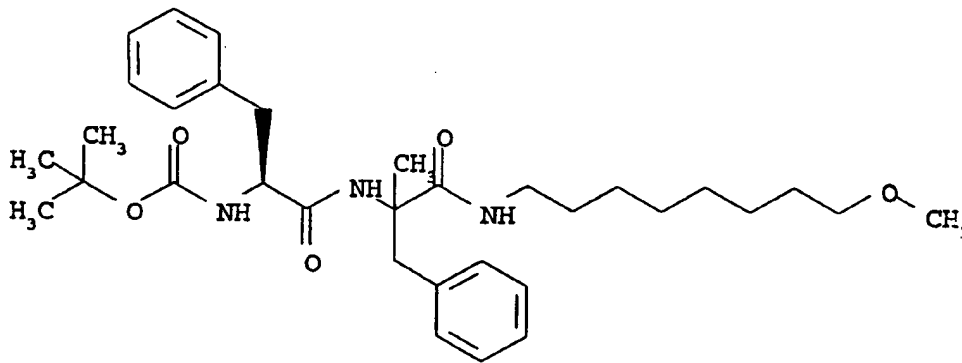
Analysis calculated for $\text{C}_{29}\text{H}_{39}\text{N}_3\text{O}_4 \cdot 0.25\text{H}_2\text{O}$:

C, 69.92; H, 7.99; N, 8.44.

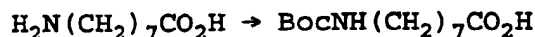
Found: C, 69.98; H, 8.09; N, 8.56.

EXAMPLE 8

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-(8-methoxyoctyl)- α -methyl-



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Step 15 BocNH(CH₂)₇CO₂H

Di-tert-butyl dicarbonate (1.7 g, 7.85 mmol) in dioxan (7 mL) was added dropwise over 5 minutes to a stirred solution of 8-aminocaprylic acid (1 g, 6.28 mmol) in 1N NaOH (7 mL) and dioxan (7 mL)
10 containing Na₂CO₃ (0.83 g, 7.85 mmol). The resulting mixture was stirred overnight at room temperature. The mixture was diluted with water (25 mL) and the dioxan was removed in vacuo. The solution was extracted once with ether (25 mL) and the pH of the aqueous solution
15 was then adjusted to four with 5% citric acid. The product was then extracted into ether (3 x 50 mL). The combined ether extracts were dried over MgSO₄, filtered, and the solvent was removed in vacuo to give a white solid, 1.61 g (99% yield), mp 56°C;
20 IR (film): 3366, 2974, 2939, 2857, 2689, 1698, and 1524 cm⁻¹;
NMR (CDCl₃): δ 1.28-1.33 (7H, m, 3CH₂, CHH), 1.45 (10H, s, CHH, C(CH₃)₃), 1.58-1.65 (2H, m, CH₂), 2.34 (2H, t, J = 7.4 Hz, CH₂COOH), 3.05-3.15 (2H, m, CH₂NHCOO),
25 4.60 (0.5H, b, 0.5 NHCOO), 5.80 (0.5H, b, 0.5NHCOO);

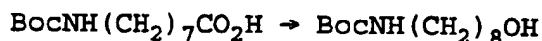
Analysis calculated for C₁₃H₂₅NO₄:

C, 60.21; H, 9.72; N, 5.40.

Found: C, 60.19; H, 9.59; N, 5.32.

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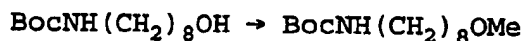
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Step 25 BocNH(CH₂)₈OH

Ethyl chloroformate (0.72 mL, 7.5 mmol) in anhydrous THF (22 mL) was added dropwise over 20 minutes to a stirred solution of BocNH(CH₂)₇CO₂H (1.74 g, 6.71 mmol) and N-methyl morpholine (0.84 mL, 7.5 mmol) in anhydrous THF (50 mL cooled in an ice bath). After 1 hour, the N-methyl morpholine salt was filtered off and 2.0 M LiBH₄ (10.3 mL, 20.6 mmol) was added dropwise over 10 minutes. The resulting mixture was stirred with a slow rewarming to room temperature for 3 hours. The solvent was removed in vacuo and the mixture was redissolved in EtOAc. This was then washed with water and brine. The organic phase was dried over MgSO₄ and the solvent removed in vacuo to give a white solid 0.158 g (62% yield), mp 54.5-55.3°C;

20 IR (film): 3367, 2931, 2854, 1687, 1524, and 1171 cm⁻¹;

25 NMR (CDCl₃): δ 1.31-1.63 (2H, m, BocCH₃ × 3, 6 × CH₂OH), 3.09 (1H, m, CH₂NCOO), 3.63 (1H, t, J = 6.6 Hz, CH₂, OH), 4.51 (1H, s, urethane).

Step 330 BocNH(CH₂)₈OMe

To a vigorously stirred mixture of BocNH(CH₂)₈OH (392 mg, 1.6 mmol) and fluoro-boric acid (210 μL, 1.6 mmol) in DCM (8 mL), the TMS CHN₂ (800 μL, 1.6 mmol) was added dropwise at 0°C. The solution was stirred at 0°C and three further additions of TMS CHN₂ (400 μL, 0.8 mmol and 200 μL × 2, 0.4 mmol) were added

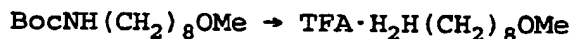
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at 15-minute intervals. The mixture was stirred for a further 4 hours after which starting material was still visible by t.l.c. but no further evolution of the reaction was however apparent.

5 The reaction was diluted with water and extracted with DCM (X3). The combined extracts were washed with water (X3), then dried over MgSO_4 , and solvent removed in vacuo. The product was purified by flash chromatography 1% to 5% MeOH/DCM, 212 mg (54% yield);
10 NMR (CDCl_3): δ 1.25-1.58 (21H, m, $\text{BocCH}_3 \times 3$, $\text{CH}_2 \times 6$), 3.04-3.18 (2H, m, CH_2N), 3.30-3.39 (5H, m, $\text{CH}_2 \text{OCH}_3$), 4.52 (1H, brs, urethane NH).

15 Step 4



$\text{TFA} \cdot \text{H}_2\text{N}(\text{CH}_2)_8\text{OMe}$

20 $\text{BocNH}(\text{CH}_2)_8\text{OMe}$ (212 mg, 0.86 mmol) was dissolved in TFA (1 mL) and DCM (1 mL) and the solution was stirred at room temperature for 1 hour. The solvent was removed in vacuo, washing with DCM $\times 3$, removing in vacuo to give 299 mg containing 1.6 equivalent of TFA;
25 NMR (CDCl_3): δ 1.31 (8H, s, $\text{CH}_2 \times 4$), 1.57-1.75 (4H, m, $\text{CH}_2 \times 2$), 2.98-3.15 (2H, m, CH_2NH), 3.37 (3H, 2 \times s, OMe), 3.44 (2H, t, CH_2OMe), 7.46 (2H, s, amine salt), 10.4 (2H, s, acid).

30 Step 5



$\text{BocSPheRSOMePheNH}(\text{CH}_2)_8\text{OMe}$

35 BocSPheRSOMePheOH (II, prepared, Example 4, Step 3) (200 mg, 0.5 mmol) and HBTU (190 mg, 0.5 mmol)

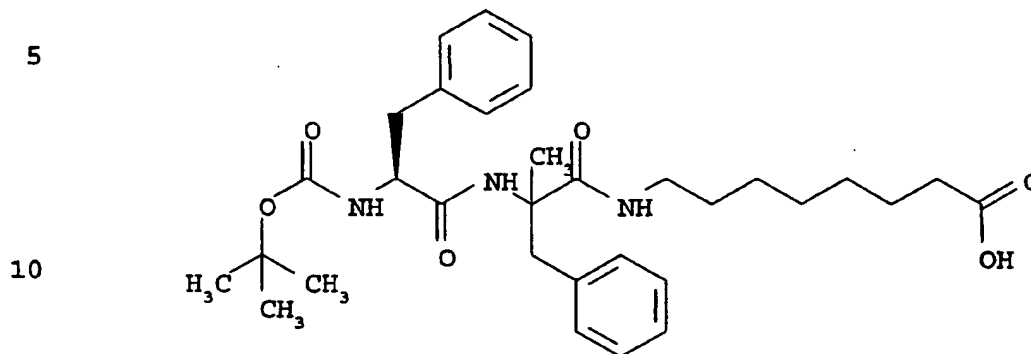
- 70 -

were dissolved in DMF (3 mL) and DIPEA (99 μ L, 0.57 mmol) was added. The solution was stirred at room temperature for 10 minutes. The TFA \cdot H₂N(CH₂)₈OMe (164 mg, 0.48 mmol) and the remaining DIPEA (199 μ L, 1.1 mmol) was then added and the solution was stirred for a further 17 hours at room temperature. The solvent was removed in vacuo and the residue was redissolved in EtOAc. The organic was washed with dilute HCl, NaHCO₃, water, and then dried over MgSO₄, the solvent was removed in vacuo, and the residue was purified by flash chromatography 1% MeOH/DCM to give a white solid 101 mg (36% yield), mp 76-81°C; IR (film): 3312, 2977, 2931, 2857, 1686, 1649, and 1528 cm⁻¹; MS FAB: MH⁺ 568; NMR (CDCl₃): δ 1.28-1.60 (24H, m, BocCH₃ \times 3, α CH₃, CH₂ \times 6), 3.32-3.38 (11H, m, β CH₂ \times 2, OCH₃, CH₂OCH₃, CONHCH₂), 3.94-4.12 (1H, m, α CH), 4.82-4.91 (1H, m, urethane NH), 5.86, 6.18 (1H, 2 \times s, amide NH), 6.49, 6.65 (1H, 2 \times s, amide NH), 6.94-6.98 (2H, m, aromatics), 7.21-7.26 (8H, m, aromatics); HPLC: 40-100% B over 20 minutes, A = H₂O, B = CH₃CN, 0.1% TFA, R_t = 18.11 minutes, >95% purity.; Analysis calculated for C₃₃H₄₉N₃O₅ \cdot 0.25H₂O: C, 69.26; H, 8.72; N, 7.34. Found: C, 69.27; H, 8.81; N, 7.31.

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EXAMPLE 9

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-(7-carboxyheptyl)- α -methyl-

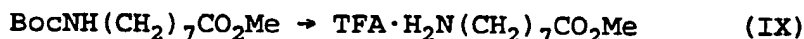
Step 1BocNH(CH₂)₇CO₂Me

BocNH(CH₂)₇CO₂H (prepared, Example 8, Step 1) (300 mg, 1.2 mmol) was dissolved in methanol (5 mL) and DCC (239 mg, 1.2 mmol) was then added. The solution was stirred at room temperature overnight. The DCU was removed by filtration and the solvent was removed in vacuo. The residue was then taken up in EtoAc and washed with dilute HCl (200 mL x 3), water (200 mL x 3), and then dried over MgSO₄, filtered, and the solvent was removed in vacuo to yield an oil, 0.259 g (79% yield);

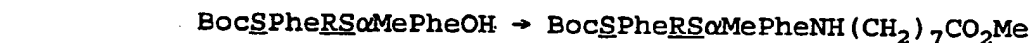
IR (film): 3368, 2932, 2858, 1739, 1715, and 1520 cm⁻¹;

NMR (CDCl₃): δ 1.31 (6H, s, CH₂ x 3), 1.44 (11H, s, BocCH₃ x 3, CH₂), 1.43 (2H, br t, CH₂), 2.30 (2H, t, J = 7.5 Hz, CH₂CO₂R), 3.09 (2H, m, CH₂NCO), 3.67 (3H, s, OCH₃), 4.57 (1H, br s, NH).

- 72 -

Step 25 TFA · H₂N(CH₂)₇CO₂Me

BocNH(CH₂)₇CO₂Me (200 mg, 0.73 mmol) was dissolved in TFA (2 mL) and DCM (2 mL) and the mixture was stirred at room temperature for 1 hour. The solvent was then removed in vacuo and the residue was dried to give an oil, 192 mg (91% yield);
10 IR (film): 3436, 2939, and 1682 cm⁻¹;
NMR (CDCl₃): δ 1.32 (6H, br s, CH₂ × 3), 1.60 (4H, m, CH₂ × 2), 2.30 (2H, t, J = 7.4 Hz, CH₂CO₂CH₃), 2.93 (2H, br, CH₂NHCO), 3.66 (3H, s, OCH₃), 5.38 (1H, br s, NH).
15

Step 3BocSPheRS_αMePheNH(CH₂)₇CO₂Me

BocSPheRS_αMePheOH (II, prepared, Example 4, Step 3) (200 mg, 0.5 mmol) was dissolved in DCM (3 mL) and HBTU (190 mg, 0.5 mmol) and DIPEA (87.6 μL, 0.5 mmol) were added. The solution was stirred for
25 10 minutes at room temperature. TFA · H₂N(CH₂)₇CO₂Me (80 mg, 0.5 mmol) and the remaining DIPEA (175.4 μL, 1.0 mmol) were added and the solution was stirred overnight at room temperature. The solvent was removed
30 in vacuo and the residue was redissolved in EtOAc. The organic phase was washed with 10% NaHCO₃, dilute HCl, water, and dried over MgSO₄. The solvent was removed in vacuo and the residue was purified by reverse phase chromatography 80% MeOH/H₂O to give a white solid,
35 211 mg (73% yield), mp 120-123°C;

- 73 -

IR (film): 3339, 3030, 2933, 2857, 1738, 1690, 1651, and 1524 cm^{-1} ;

MS (CI): 583 (MH^+), 582, (M^+), 482, 174, and 134);

NMR (CDCl_3): δ 1.11-1.62 (22H, m, $\text{BocCH}_3 \times 3$, αCH_3 ,

5 $\text{CH}_2 \times 5$), 2.29 (2H, t, $J = 7.5$ Hz, $\text{CH}_2\text{CO}_2\text{Me}$), 2.78-3.44 (6H, m, $\beta\text{CH}_2 \times 2$, CH_2NCO), 3.65 (3H, s, OCH_3), 4.01-4.13 (1H, m, αCH), 5.00, 5.12 (1H, 2 \times br d, urethane NH), 5.99, 6.35 (1H, 2 \times s, amide NH), 6.71, 6.81 (1H, 2 \times br s, amide NH), 6.96 (2H, m, aromatics), 7.17-7.36 (8H, m, aromatics);

10 HPLC: 40-100% B over 20 minutes, A = H_2O , 0.1% TFA, B = CH_3CN , 0.1% TFA; $R_t = 17.27$ minutes, 97% purity.

Analysis calculated for $\text{C}_{33}\text{H}_{47}\text{N}_3\text{O}_6 \cdot 0.3\text{H}_2\text{O}$:

C, 67.50; H, 8.17; N, 7.16.

15 Found: C, 67.53; H, 8.25; N, 7.21.

Step 4



$\text{BocSPheRS}\alpha\text{MePheNH}(\text{CH}_2)_7\text{CO}_2\text{H}$

$\text{BocSPheRS}\alpha\text{MePheNH}(\text{CH}_2)_7\text{CO}_2\text{Me}$ (91 mg, 0.16 mmol) was dissolved in dioxan (1 mL) and LiOH (320 μL , 0.32 mmol) was added. The reaction was stirred at room temperature for 3.5 hours. The solvent was removed in vacuo and the residue was dissolved in water. The aqueous was washed once with ether and the pH was adjusted to three with dilute HCl. The product was then extracted into ether and the organic layer was dried over MgSO_4 , filtered, and the solvent was removed in vacuo to give a white solid 79 mg (87% yield), mp 52-53.5°C;

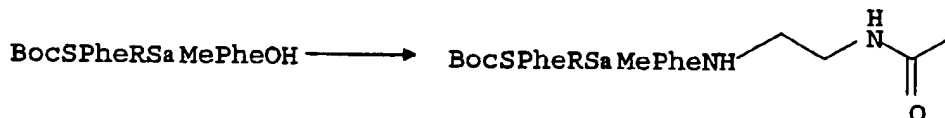
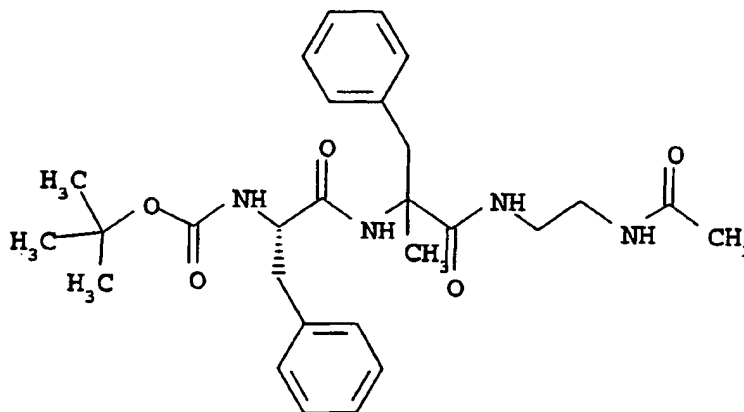
30 IR (film): 3326, 2932, 2858, 1709, 1651, and 1520 cm^{-1} ;

-74-

NMR (CDCl₃): δ 1.25-1.58 (22H, m, CH₃ \times 3, α CH₃,
 CH₂ \times 5), 2.34 (2H, t, J = 7.3 Hz, CH₂NHCO), 2.89-3.38
 (6H, m, β CH₂ \times 2, CH₂CO₂H), 4.00-4.19 (1H, m, α CH),
 4.92-5.10 (1H, 2 \times br d, urethane NH), 5.92, 6.22 (1H,
 2 \times s, amide NH), 6.55, 6.68 (1H, 2 \times br s, amide NH),
 6.96 (2H, m, aromatics), 7.19-7.33 (8H, m, aromatics);
 MS (CI): 569 MH⁺, 568 (M⁺), 468, 160, and 134;
 HPLC: 40-100% B over 20 minutes, A = H₂O, 0.1% TFA,
 B = CH₃CN, 0.1% TFA; R_t = 13.7 minutes, 95% purity;
 Analysis calculated for C₃₂H₄₅N₃O₆ \cdot 0.6H₂O:
 C, 66.44; H, 7.94; N, 7.26.
 Found: C, 66.37; H, 8.05; N, 7.19.

EXAMPLE 10

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-[2-(acetylamino)ethyl]- α -methyl-



BocSPheRSaMePheOH (II, prepared Example 4, Step 3)
 (0.20 g, 0.5 mmol), HBTU (0.19 g, 0.5 mmol) and DIPEA
 (88 μ L, 0.5 mmol) were dissolved in DMF (5 mL) and the
 solution was stirred for 10 minutes. The
 N-acetylenediamine (0.62 g, 0.6 mmol) and the
 remaining DIPEA (88 μ L, 0.5 mmol) were added and the

-75-

solution was stirred overnight. The solution was concentrated in vacuo and the residue was redissolved in EtOAc (50 mL). The solution was washed sequentially with dilute HCl (3 x 50 mL), saturated NaHCO₃

5 (3 x 50 mL), water (3 x 50 mL), and brine (2 x 50 mL).

The organic phase was dried over MgSO₄, filtered, and concentrated in vacuo. The residue was purified by medium pressure silica chromatography, eluting with 1% MeOH in DCM to give 240 mg (96% yield) as a white foam, mp 72-74°C;

10 IR (film): 3307, 2979, 1685, 1654, and 1533 cm⁻¹;

MS (CI): 511 (MH⁺);

$[\alpha]_D^{24} = -24.9^\circ$ (C = 0.5 MeOH);

NMR (CDCl₃): δ 1.32, 1.36 (9H, 2 x s, BocCH₃), 1.47, 1.54 (3H, 2 x s, α CH₃), 1.96, 1.99 (3H, 2 x s, NCOCH₃), 2.13-3.38 (8H, m, β CH₂ x 2, CH₂ x 2), 4.00 (1H, m, α CH), 4.93, 5.04 (1H, 2 x br d, urethane NH), 6.06, 6.20 (1H, 2 x s, amide NH), 6.50 (1H, 2 x br s, amide NH), 6.95 (3H, m, 2 x aromatics, amide NH), 7.16-7.34 (8H, m, aromatics);

20 Analysis calculated for C₂₈H₃₈N₄O₅·0.5H₂O:

C, 64.72; H, 7.56; N, 10.78.

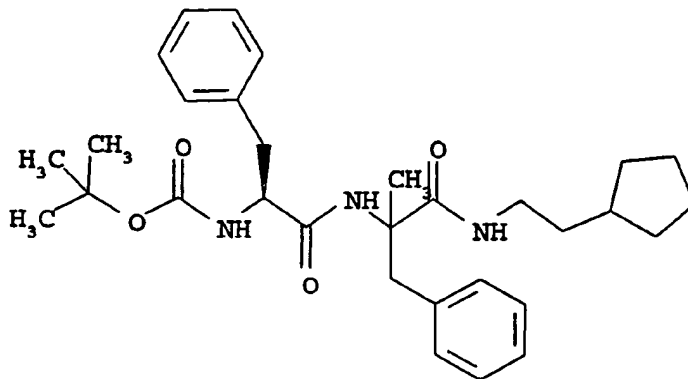
Found: C, 64.75; H, 7.44; N, 10.73.

25

EXAMPLE 11

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-(2-cyclopentylethyl)- α -methyl-

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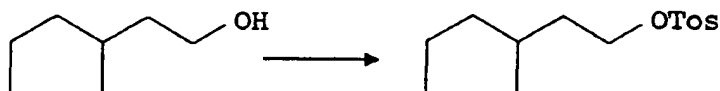


35

-76-

Step 1

5



2-Cyclopentyl ethanol (1.0 g, 8.76 mmol) was dissolved in pyridine (10 mL) and tosyl chloride (1.90 g, 10 mmol) was added. The reaction was stirred at room temperature overnight. The reaction mixture was diluted with EtoAc and washed with dilute HCl, NaHCO₃, and H₂O. The organic phase was dried over MgSO₄ and the solvent was removed in vacuo to give an oil. The product was purified by medium pressure chromatography 0-100% EtoAc/Hexane to give an oil, 1.02 g (43% yield);

IR (film): 2950, 1599, 1335, and 1179 cm⁻¹;

MS (CI): 269 (MH⁺) and 537 (M²⁺);

NMR (CDCl₃): δ 0.96-1.07 (2H, m, CH₂), 1.45-1.83 (9H, m, CH₂ \times 4, CH), 2.45 (3H, s, CH₃), 4.04 (2H, t, J = 6.6 Hz, CH₂OTos), 7.34 (2H, d, J = 8.3 Hz, aromatics, H_{3,5}), 7.79 (2H, d, J = 8.3 Hz, aromatics, H_{2,6});

HPLC: 40-100% B over 30 minutes; A = H₂O, 0.1% TFA; B = CH₃CN, 0.1% TFA; R_t = 18.91 minutes >98% purity;

Analysis calculated for C₁₄H₂₀O₃S:

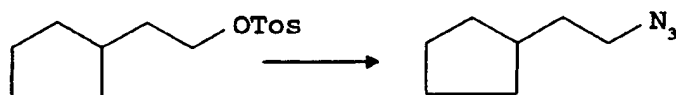
C, 62.66; H, 7.51.

Found: C, 62.52; H, 7.56.

-77-

Step 2

5

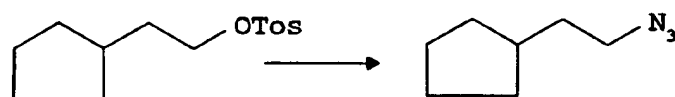


The tosylate (Step 1) (0.803 g, 3 mmol) was dissolved in DMF (10 mL) and sodium azide (0.251 g, 3.3 mmol) was added. The solution was stirred at room temperature overnight and then poured onto ice. The ice was then extracted with EtoAc and the combined extracts washed with brine. The solvent was then removed in vacuo to give a clear oil, 0.255 g (61% yield);

IR (film): 2950, 2869, and 2096 cm⁻¹;
NMR (CDCl₃): δ 1.08-1.14 (2H, m, CH₂), 1.52-1.86 (9H, m, CH₂ \times 4, CH), 3.27 (2H, t, J = 7.2 Hz, CH₂N₃).

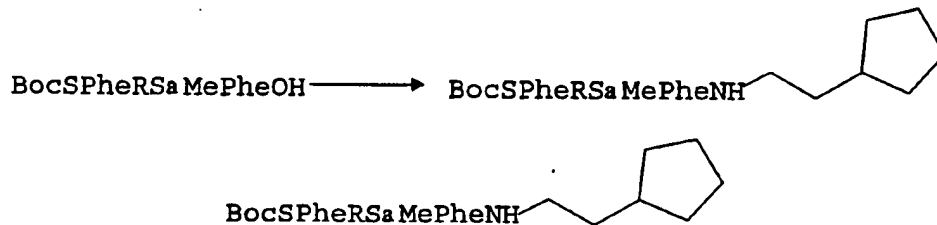
Step 3

20



The azide (Step 2) (0.255 g, 1.8 mmol) was dissolved in ethanol (20 mL) and Lindlar catalyst (50 mg) was added. The solution was hydrogenated at 40 psi, 30°C for 2.5 hours. The catalyst was removed by filtration through celite and the solvent was removed in vacuo to give a residue (44 mg). The residue was used without purification.

- 78 -

Step 4

10 BocSPheRSaMePheOH (II, prepared, Example 4, Step 3) (166 mg, 0.39 mmol) and HBTU (148 mg, 0.39 mmol) were dissolved in DMF (3 mL), DIPEA (68 μ L, 0.39 mmol) was added and the solution was stirred for 10 minutes. The amine (Step 3) (44 mg, 0.39 mmol) and the remaining DIPEA (69 μ L, 0.39 mmol) were added and

15 the reaction was stirred over the weekend. The solvent was removed in vacuo and the residue was redissolved in EtOAc. The organic phase was then washed with dilute HCl, 10% NaHCO₃, water, and then dried over MgSO₄. The solvent was then removed in vacuo to give a brown oil

20 which was purified by medium pressure chromatography 20% MeOH/DCM to give a white solid 85 mg (42% yield), mp 119-123°C;

IR (film): 3887, 3826, 3344, 2949, 1672, 1688, 1640, and 1523 cm⁻¹;

25 $[\alpha]_D^{21.0} = -20.4^\circ$ (C = 0.265 in MeOH);

MS (CI): 522 (M⁺), 422, and 134;

HPLC: 40-100% B over 20 minutes, A = H₂O 0.1% TFA, B = CH₃CN, 0.1% TFA, R_t = 19.0 minutes >95% purity;

30 NMR (CDCl₃): δ 1.07 (2H, m, CH₂), 1.33, 1.37 (9H, 2 \times s, BocCH₃ \times 3), 0.92-1.74 (12H, m, α CH₃, CH₂ \times 4, CH), 2.75-3.43 (6H, m, β CH₂ \times 2, CH₂NCO), 4.00-4.11 (1H, m, α CH), 4.82-4.90 (1H, 2 \times br d, urethane NH), 5.87, 6.20 (1H, 2 \times s, amide NH), 6.47, 6.60 (1H, 2 \times s, amide NH), 6.95 (2H, m, aromatics), 7.16-7.36

35 (8H, m, aromatics);

-79-

Analysis calculated for $C_{31}H_{43}N_3O_4$:

C, 71.37; H, 8.31; N, 8.05.

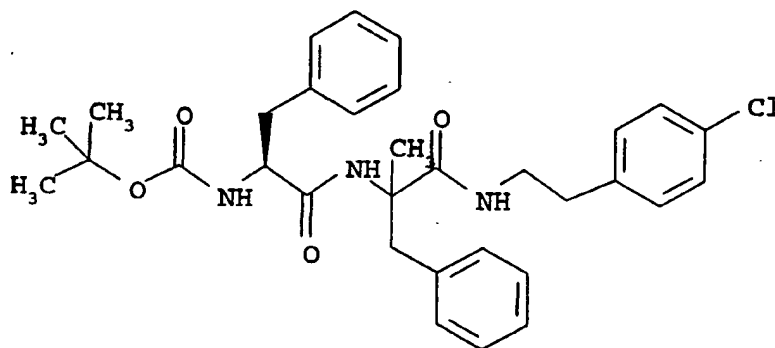
Found: C, 71.40; H, 8.29; N, 8.01.

5

EXAMPLE 12

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-[2-(4-chlorophenyl)ethyl]- α -methyl-

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To a stirred solution of Boc(L)Phe(DL) α MePhe (II, prepared, Example 4, Step 3) (0.20 g, 0.47 mmol) in dimethylformamide (5 mL) was added HBTU (0.18 g, 0.47 mmol), diisopropylamine (0.12 g, 0.94 mmol) and 2-(4-chlorophenyl)ethylamine (0.073 g, 0.47 mmol). The reaction was stirred at room temperature for 20 hours. The dimethylformamide was removed in vacuo and the residue taken up in ethyl acetate. The organic layer was washed with 0.1N hydrochloric acid, dried over magnesium sulphate, and the solvent removed in vacuo. Purification by column chromatography gave the product, 0.175 g (66%), mp 161-164°C;

IR (film): 3325 (NH), 2979 (CH), 1684 (C = O urethane), 1653 (amide I), and 1494 (amide II);

NMR ($CDCl_3$): 1.33, 1.36 (9H, 2 x s, $(CH_3)_3C$), 1.45, 1.53 (3H, 2 x s, αCH_3), 2.73-3.44 (8H, m, CH_2 x 4), 3.90-4.15 (1H, m, αCH), 4.75-4.90 (1H, m, urethane NH), 5.81, 6.10 (1H, 2 x s, amide NH), 6.60-6.70, 6.70-6.80 (1H, 2 x m, amide NH), 6.90-6.98 (2H, m, aromatics), 7.06-7.33 (12H, m, aromatics);

-80-

Analysis calculated for $C_{32}H_{38}ClN_3O_4$:

C, 68.13; H, 6.79; N, 7.45.

Found: C, 67.85; H, 6.80; N, 7.38.

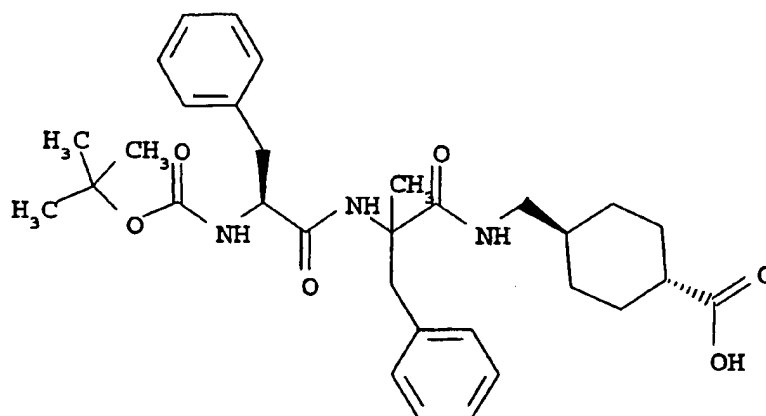
5

EXAMPLE 13

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-[(4-carboxycyclohexyl)methyl]-
 α -methyl-, trans-

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Boc(L)Phe(DL) α MePheOH (II, prepared, Example 4,
 Step 3) (0.200 g; 0.47 mmol), HBTU (0.178 g, 0.47 mmol)
 and diisopropylethylamine (0.388 mL, 1.41 mmol) were
 stirred together in DMF (5 mL) at room temperature for
 20 minutes. Trans-4-(aminomethyl)cyclohexane
 carboxylic acid was then added and the resulting
 suspension was stirred for 18 hours. On removal of
 DMF, the residue was partitioned between water and
 ethyl acetate. The organic layer was washed with 2 M
 HCl and further purified by reverse phase column
 chromatography using 50% to 90% MeOH/H₂O to give a
 white solid (0.080 g, 30%), mp 100-116°C;
 IR (film): 3335, 1705, 1670, and 1644 cm⁻¹;
 MS: (CI) 134 (100%), 566 (M + 1);
 NMR (DMSO-d₆): δ 0.75-2.10 (21H, m, Boc, α -CH₃,
 cyclohexyl), 2.65-3.35 (6H, m, 2 \times β -CH₂-, -CONHCH₂-),
 4.00-4.15 (1H, m, α H), 6.90-7.85 (13H, m, Ar, -OCCNH-,
 2 \times -CONH-);

-81-

Analysis calculated for $C_{32}H_{43}N_3O_6$:

C, 67.94; H, 7.66; N, 7.43.

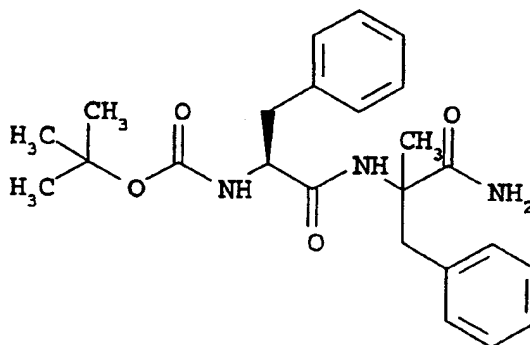
Found: C, 67.66; H, 7.60; N, 7.23.

5

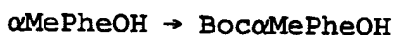
EXAMPLE 14

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl- α -methyl-

10



15

Step 1RSRS

20

The acid (1.0 g, 5.58 mmol) was stirred and dissolved in 1,4-dioxan (10 mL). To this was added H₂O (10 mL) followed by Na₂CO₃ (1.18 g, 11.16 mmol) and di-tert-butyl dicarbonate (1.46 g, 6.70 mmol) in 1,4-dioxan (3 mL). The mixture was stirred vigorously at room temperature overnight and then the 1,4-dioxan removed in vacuo. The residue was diluted with water (50 mL) and extracted with Et₂O (2 × 25 mL). The aqueous solution was made pH 3 with citric acid solution and extracted with EtOAc (3 × 25 mL). The combined EtOAc extracts were washed with water (3 × 25 mL), dried over MgSO₄, filtered, and the solvent removed in vacuo giving the product as a white solid (1.06 g, 68%);

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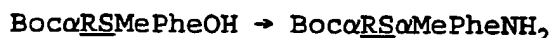
IR (film): 2982, 1713, 1498, 1453, and 1369 cm⁻¹;

NMR (DMSO-d₆): δ 1.19 (3H, s, CH₃), 1.41 (9H, s, C(CH₃)₃), 2.93 (1H, d, J = 13.3 Hz, PhCHH), 3.30 (1H,

-82-

d, obscured by H₂O, PhCHH), 6.66 (1H, bs, OCONH), 7.10 (2H, d, J = 7.2 Hz, Ph), 7.18-7.29 (3H, m, Ph), 12.5 (1H, bs, COOH).

5 Step 2

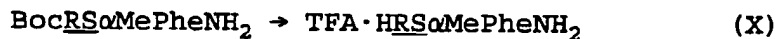


Et₃N (0.598 g, 5.9 mmol) was added to a stirred
 10 solution of the acid (1.50 g, 5.37 mmol) in EtOAc (25 mL) and the mixture cooled to -10°C. Isobutylchloroformate (0.807 g, 5.91 mmol) in EtOAc (5.0 mL) was added dropwise over 5 minutes and the mixture stirred at room temperature for 30 minutes.
 15 The mixture was filtered and ammonia gas bubbled through the stirred solution for 35 minutes. The solid precipitate was filtered off giving the product as a white solid (0.794 g, 53%);
 NMR (DMSO-d₆): δ 1.33 (3H, s, CH₃), 1.41 (9H, s, (CH₃)₃C), 3.18 (2H, s, CH₂), 6.25 (1H, bs, CONHN),
 20 (CH₃)₃C), 3.18 (2H, s, CH₂), 6.25 (1H, bs, CONHN),

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{C}_6\text{H}_5, \text{OCNH} \end{array}$$

 7.07-7.26 (6H, m, C₆H₅, OCNH), 7.42 (1H, bs, CONHH).

25 Step 3



The amide (0.60 g, 2.16 mmol) was stirred and
 30 suspended in anhydrous CH₂Cl₂ (4 mL) and trifluoroacetic acid (5 mL) added. The mixture was stirred for 50 minutes and then the solvent removed in vacuo. The residue was triturated with Et₂O, filtered, and the solid dried under vacuum to give the
 35 product as a white powder (0.601 g, 95%);
 IR (film): 3401, 3313, 1659, and 1525 cm⁻¹;

-83-

NMR (DMSO- d_6): δ 1.48 (3H, s, CH_3), 3.02 (1H, d, $J = 14.0$ Hz, PhCHH), 3.16 (1H, d, $J = 14.0$ Hz, PhCHH), 7.21-7.34 (5H, m, C_6H_5), 7.70 (1H, s, CONHH), 7.89 (1H, s, CONHH), 8.00 (3H, bs, N^+H_3).

5 TFA- α -MePheNH₂ (XI) was prepared by an analogous procedure;

NMR (DMSO- d_6): δ 1.48 (3H, s, αCH_3), 3.02 (1H, d, $J = 14.0$ Hz, βCH), 3.16 (1H, d, $J = 14.0$ Hz, βCH), 7.20-7.35 (5H, m, aromatics), 7.69, 7.89 (1H, 2 x s, CONH_2), 8.02 (3H, bs, NH_3^+).

Step 4

15 BocSPheOH + TFA-HR α -MePheNH₂ \rightarrow BocSPheR α -MePheNH₂

Diisopropylethylamine (0.362 g, 2.80 mmol) in DMF (1 mL) was added to a stirred solution of the acid (0.248 g, 0.93 mmol) and HBTU (0.354 g, 0.94 mmol) in DMF (5 mL) and the mixture stirred for 15 minutes at room temperature. The TFA salt (0.30 g, 1.03 mmol) in DMF (5 mL) was then added dropwise over 5 minutes and the reaction stirred at room temperature for 30 minutes. The solvent was removed in vacuo and the residue purified by chromatography on silica using EtOAc as eluant. This gave the product as a white amorphous solid (0.188 g, 47%), mp 141-143°C; IR (film): 3300, 2981, 1666, and 1497 cm^{-1} ; NMR (DMSO- d_6): δ 1.30 (9H, s, $\text{C}(\text{CH}_3)_3$), 1.42 (3H, s, CH_3), 2.72-2.80 (1H, m, PhCHH), 2.96-3.07 (1H, m, PhCHH), 3.15-3.40 (2H, m, PhCH_2), 4.04-4.20 (1H, m, CH_2CH), 6.80-7.27 (3H, m, $2\text{C}_6\text{H}_5$, CONH_2 , OCONH), 7.57 (1H, s, CONH);

Analysis calculated for $\text{C}_{24}\text{H}_{31}\text{N}_3\text{O}_4 \cdot 0.1\text{H}_2\text{O}$.

35

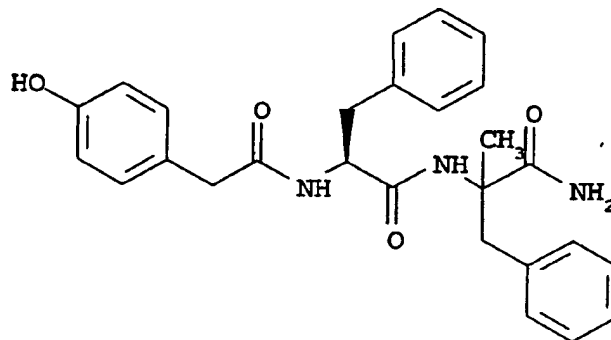
-84-

EXAMPLE 15

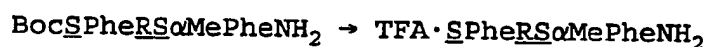
DL-Phenylalaninamide, N-[(4-hydroxyphenyl)acetyl]-
L-phenylalanyl- α -methyl-

5

10

Step 1

15

TFA \cdot (L) Phe (D, L) α -Me-Phe-NH₂

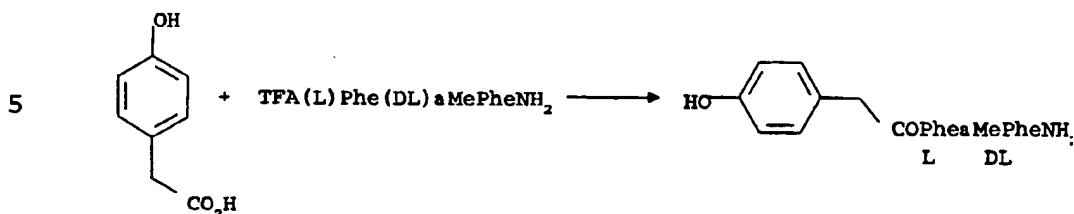
Boc(L)Phe(D,L) α MePheNH₂ (Example 14, Step 4)
 (8.90 g, 0.032 mol) was stirred in cold trifluoroacetic
 acid for 10 minutes. The solution was evaporated down
 to an oil and then triturated with diethyl ether to
 give a white solid (9.26 g, 99%), mp 272-276°C;
 ν_{max} (film)/cm⁻¹: 3223br (NH), 3032 (NH of +NH₃), 2926
 (Al-H), 1679 (CO amide), 1670 (CO amide), and 1530
 (CO amide);

25

δ_{H} (DMSO): 1.28, 1.36 (3H, 2s, CH₂CCH₃), 3.0 (2H, m,
 PhCH₂CH), 3.20 (2H, m, PhCH₂C), 4.13 (1H, m, PhCH₂CH),
 7.2 (13H, m, H_{arom}, NH, NH₂), 8.14 (3H, d, J = 13 Hz,
 +NH₃).

30

- 85 -

Step 2

4-Hydroxyphenylacetic acid (69 mg, 0.45 mmol) and
 10 HBTU (172 mg, 0.45 mmol) were stirred together in DMF
 (5 mL) for 20 minutes. TFA·(L)Phe(DL)αMePheNH₂
 (200 mg, 0.45 mmol) and diisopropylethylamine
 (0.257 mL, 1.48 mmol) in DMF (5 mL) were added and the
 solution was stirred for 18 hours at room temperature.
 15 On removal of the DMF, the residue was dissolved in
 ethyl acetate and washed with 10% citric acid solution,
 10% Na₂CO₃ solution, and water. Purification by
 prepared HPLC using 20% to 80% CH₃CN/H₂O +0.1% TFA·
 gave a white solid (50 mg, 24%), 30:70 mixture of
 20 diastereoisomers by HPLC (95% pure);
 IR (film: 3261, 1680, and 1645 cm⁻¹;
 NMR (DMSO-d₆): δ 1.28 (1/2 × 3H, s) and 1.35
 (1/2 × 3H, s, αCH₃), 2.70-3.45 (6H, m, 4 × β-CH₂- and
 benzyl CH₂), 4.33 (1/2 × 1H, m) and 4.48 (1/2 × 1H, m,
 25 αH), 6.56-7.29 (16H, m, Ar, -CONH₂), 7.69 (1H, s,
 -CONH-), 8.26 (1/2 × 1H, d, J = 8.4 Hz) and 8.33
 (1/2 × 1H, d, J = 7.4 Hz, -CONH-), 9.13 (1H, s, -OH).

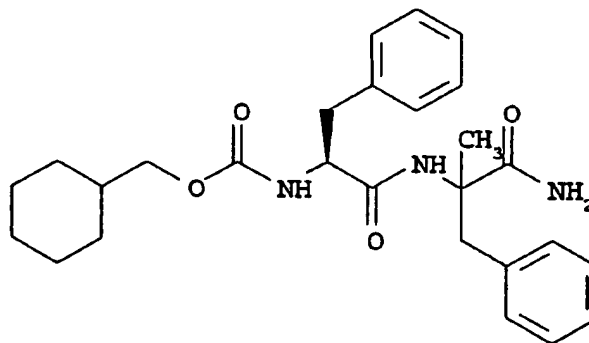
-86-

EXAMPLE 16

DL-Phenylalaninamide, N-[(cyclohexylmethoxy)carbonyl]-
L-phenylalanyl- α -methyl-

5

10



Pyridine (0.069 mL, 0.85 mmol) in DCM (1 mL) was added dropwise to a solution of triphosgene (0.092 g, 0.31 mmol) and cyclohexylmethanol (0.105 mL, 0.85 mmol) in DCM (4 mL) at 0°C. The solution was stirred for 5 minutes. The mixture was evaporated down to a white solid, taken up in ethyl acetate (~10 mL), and filtered. The filtrate was added to a solution of TFA(L)Phe(DL) α MePhNH₂ (0.150 g, 0.34 mmol) and triethylamine (0.094 mL, 0.68 mmol) in DMF (3 mL) and allowed to stir for 18 hours at room temperature. On removal of the solvents, the residue was partitioned between water and ethyl acetate. The organic layer was washed with 10% citric acid solution, 10% Na₂CO₃ solution, and water. Further purification by reverse phase chromatography using 60% to 90% MeOH/H₂O gave a white solid (0.120 g, 76%);

IR (film): 3305 cm⁻¹ and 1665 cm⁻¹;
M/e (CI): 466 (M+1) and 134 (100%);
NMR (DMSO-d₆): δ 0.83-1.60 (14H, m, cyclohexyl, α CH₃),

2.47-3.37 (4H, m, β -CH₂- 's), 3.67 (2H, m, (-CH₂OC-),
4.09 (1/2 \times 1H, m), and 4.19 (1/2 \times 1, m, α H),
7.05-7.73 (14H, m, Ar, -CONH₂, -CONH-, -OCONH-);

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Analysis calculated for $C_{27}H_{35}N_3O_4$:

C, 69.65; H, 7.58; N, 9.03.

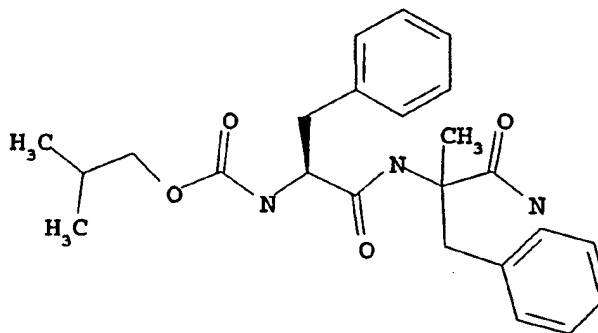
Found: C, 69.35; H, 7.62; N, 8.84.

5

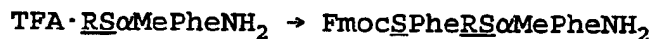
EXAMPLE 17

DL-Phenylalaninamide, N-[(2-methylpropoxy)carbonyl]-
L-phenylalanyl- α -methyl-

10



15

Step 1

20

Fmoc(L)Phe(D,L) α MePheNH₂

Fmoc(L)PheOpfp (8.60 g, 0.0155 mol),
TFA \cdot (DL) α MePheNH₂ (X) (4.80 g, 0.0162 mol), and
triethylamine (2.27 mL, 0.0162 mol) in N,N-dimethyl-
formamide (200 mL) were stirred together over a
weekend. The solvent was evaporated off under pressure
and the resulting thick yellow oil diluted in H₂O
(250 mL). This was extracted into ethyl acetate and
the resulting organic solution washed with H₂O, 10%
citric acid, 10% sodium carbonate, brine and H₂O in
turn, dried over magnesium sulphate, and evaporated
down to a yellow foam. The product was purified by
flash chromatography (2% methanol in CH₂Cl₂), followed
by washing with petroleum ether to give a pale yellow
solid (6.70 g, 79%), mp 83-85°C;

30

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ν_{\max} (film)/ cm^{-1} : 3306 (NH), 3031 (ar-H), 2931 (Ali-H), 1667 (CO amide), 1604 (C = C Ar), and 1533 (CO amide);

5 δ_{H} (DMSO): 1.37, 1.39 (3H, 2s, CH_2CCH_3), 2.80 (1H, m, 1 of PhCH_2CH), 3.00 (1H, m, 1 of PhCH_2CH), 3.20 (2H, m, PhCH_2C), 4.11 (1H, m, PhCH_2CH), 7.2 (22H, m, H_{arom} , NH_2 , NH).

Step 2

10



(L) Phe (DL) α MePheNH₂

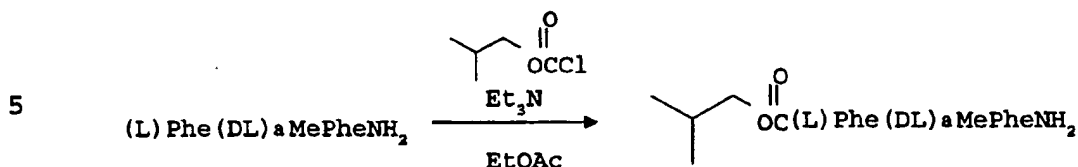
15 $\text{Fmoc(L)Phe(DL)}\alpha\text{MePheNH}_2$ (6.70 g, 0.0122 mol) was stirred in 20% piperidine in N,N-dimethylformamide (40 mL) for 20 minutes. The solvent was evaporated off under pressure and the resulting solid washed with 1:1 hexane:diethyl ether and dissolved in 10% citric acid. This was neutralized with 10% sodium carbonate solution

20 and the product extracted into ethyl acetate. The organic solution was washed with brine and H_2O in turn, dried over magnesium sulphate, and evaporated down to a pale yellow foam. This was washed with more 1:1 hexane:diethyl ether, mp 69-72°C;

25 ν_{\max} (film)/ cm^{-1} : 3308 (NH), 3029 (Ar-H), 2926 (Ali-H), and 1661 (CO amide);

30 δ_{H} (DMSO): 1.45, 1.47 (3H, 2s, CH_2CCH_3), 2.64 (1H, m, 1 of PhCH_2CH), 2.85 (1H, m, 1 of PhCH_2CH), 3.33 (2H, m, PhCH_2C), 4.42 (1H, m, PhCH_2CH), 7.2 (12H, m, H_{arom} , NH_2), 7.31, 7.41 (1H, 2s, amide NH), 8.16 (2H, s, NH_2CH).

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Step 3

Isobutyl chloroformate (0.066 mL, 0.50 mmol) was added dropwise to a solution of (L)Phe(DL)αMePheNH₂ (150 mg, 0.46 mmol) and triethylamine (0.064 mL, 0.46 mmol) in ethyl acetate (8 mL) at 0°C. The mixture was allowed to warm to room temperature and stirred for 18 hours. The resulting solution was washed with 10% citric acid solution and water. Drying (MgSO₄) and evaporation yielded a yellow oil. Further purification by flash chromatography using 2.5% MeOH/DCM and the reverse phase chromatography using 60% to 90% MeOH/H₂O gave a white solid (90 mg, 46%);

IR (film): 3308, 2960, and 1669 cm⁻¹;

M/e (FAB): 448 (M+Na);

NMR (DMSO-d₆): δ 0.81 (6H, m, 2 × CH₃), 1.37 (1/2 × 3H, s) and 1.38 (1/2 × 3H, s, αCH₃), 1.74 (1H, m, Me₂CH-), 2.70-3.36 (4H, m, 4 × β H's), 3.63 (2H, m, -CH₂OCO-), 4.13 (1H, m, αH), 7.05-7.27 (12H, m, Ar, -CONH₂), 7.42 (1/2 × 1H, d, J = 8.6 Hz), 7.54 (1/2 × 1H, d, J = 7.9 Hz, -CONH-), 7.75 (1H, d, J = 4.8 Hz, -OCONH-);

Analysis calculated for C₂₄H₃₁N₃O₄:

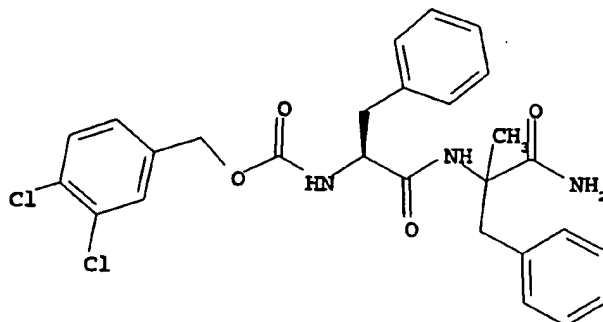
C, 67.74; H, 7.34; N, 9.87.

Found C, 67.46; H, 7.34; N, 9.81.

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EXAMPLE 18

DL-Phenylalaninamide, N-[[[(3,4-dichlorophenyl)methoxy]carbonyl]-
L-phenylalanyl- α -methyl-



Pyridine (0.097 mL, 1.2 mmol) in DCM (0.5 mL) was added dropwise to a solution of 3,4-dichlorobenzyl alcohol (212 mg, 1.2 mmol) and triphosgene (130 mg, 0.44 mmol) in DCM (2 mL) at 0°C. The mixture was stirred for 10 minutes and evaporated down to a white solid which was taken up in ethyl acetate and filtered. The filtrate was added to a solution of (L)Phe(DL) α MePheNH₂ (XII) (150 mg, 0.46 mmol) and triethylamine (0.064 mL, 0.46 mmol) in ethyl acetate and allowed to stir for 18 hours. The resulting suspension was washed with 10% citric acid solution, 10% Na₂CO₃, and water. Further purification by flash chromatography using 2% MeOH/DCM and then reverse phase chromatography using 60% to 90% MeOH/H₂O gave a white solid (120 mg, 49%);

IR (film): 3309, 1714, and 1664 cm⁻¹;

M/e (FAB): 511 (100%), 528 (M+1), and 532 (M+5);

NMR (DMSO-d₆): δ 1.35 (1/2 \times 3H, s) and 1.39 (1/2 \times 3H, s, α CH₃), 2.67-3.38 (4H, m, 4 \times β H's), 4.10-4.27 (1H, m, α H), 4.95 (2H, m, -CH₂-OCO-), 7.05-7.85 (17H, m, Ar, -CONH₂, -CONH-, -OCONH-);

Analysis calculated for C₂₇H₂₇N₃O₄Cl₂:

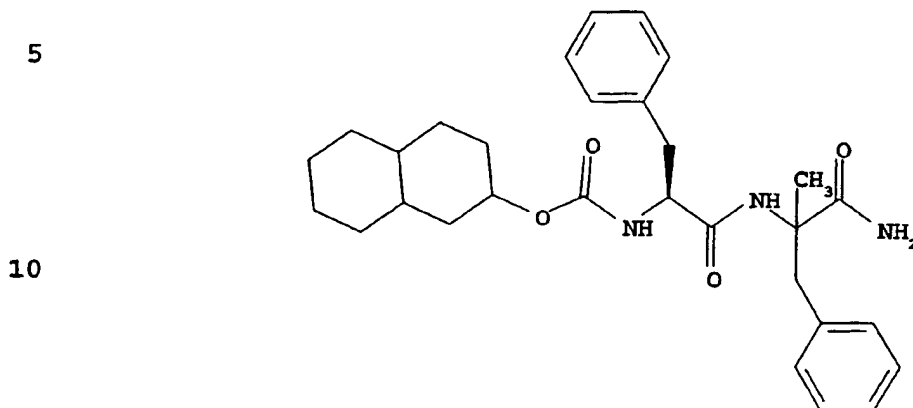
C, 61.37; H, 5.15; N, 7.95.

Found: C, 61.37; H, 5.12; N, 7.91.

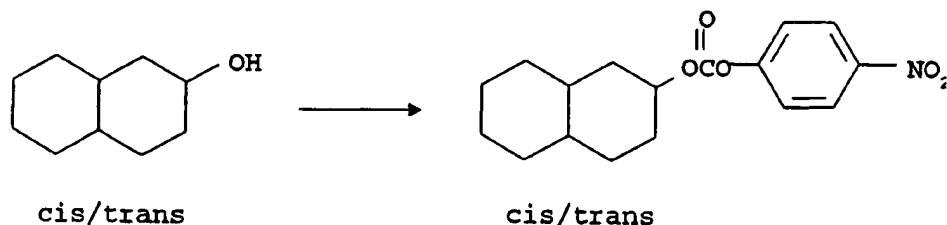
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EXAMPLE 19

DL-Phenylalaninamide, N-[[[(octahydro-2-naphthalenyl)-oxy]carbonyl]-L-phenylalanyl- α -methyl-

Step 1

15



To a stirred solution of Cis/trans decahydro-2-naphthol (1.54 g, 10 mmol) and 4-nitrophenylchloroformate (2.01 g, 10 mmol) in dichloromethane (50 mL) cooled to 0°C was added dropwise a solution of pyridine (0.79 g, 10 mmol) in dichloromethane (10 mL). The reaction was stirred overnight at room temperature. The solvent was removed in vacuo and the residue was taken up in ethyl acetate (100 mL) and 10% aqueous citric acid (10 mL). The ethyl acetate was washed with 10% citric acid, saturated aqueous sodium bicarbonate, water, and brine, dried over magnesium sulphate, and the solvent removed in vacuo. Purification by flash chromatography gave a white solid, 2.28 g (71%), mp 48-52°C;

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IR (film): 2925, 1762, 1525, and 1346 cm^{-1} ;
 NMR (CDCl_3): 0.90-2.20 (16H, m, aliphatics), 4.71,
 4.93 (1H, 2 x m CHO (cis and trans)), 7.38 (2H, d,

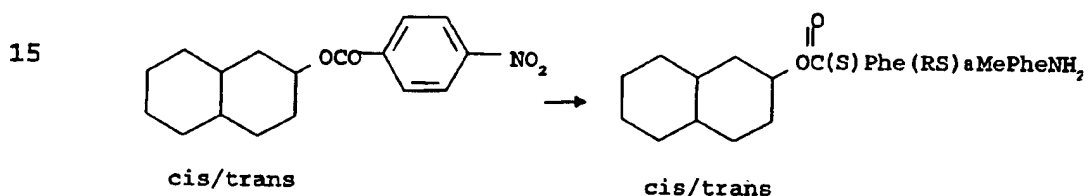
5 $J = 9.1$ Hz aromatics adjacent to $\text{OC}(=\text{O})$, 8.27 (2H, d,
 $J = 9.1$ Hz, aromatics adjacent to NO_2).

Analysis calculated for $\text{C}_{17}\text{H}_{21}\text{NO}_5$:

C, 63.94; H, 6.63; N, 4.39.

10 Found: C, 64.01; H, 6.65; N, 4.39.

Step 2



To a stirred solution of $\text{TFA} \cdot (\text{L})\text{Phe}(\text{DL})\alpha\text{MePheNH}_2$
 20 (0.2 g, 0.45 mol) and decahydronaphthyl-p-nitrophenyl
 carbonate (prepared, Example 15, Step 1) (0.16 g,
 0.5 mmol) in dimethylformamide (10 mL) was added
 dropwise triethylamine (0.101 g, 10 mmol) in dimethyl-
 formamide (5 mL). The reaction was stirred for 8 days.
 25 The dimethylformamide was removed in vacuo and the
 residue taken up in ethyl acetate. The ethyl acetate
 was washed with 2N hydrochloric acid, saturated aqueous
 sodium bicarbonate, water and brine, and dried over
 magnesium sulphate. The solvent was removed in vacuo.
 30 Purification by flash chromatography in 10% ethyl
 acetate/hexane increase to 100% ethyl acetate gave a
 white foam, 0.155 g (67%), mp 88-92°C;
 IR (film): 3307 (NH), 2924 (CH), 1690 (shoulder,
 urethane C = O), 1668 (amide I), and 1512 (amide II);
 35 $[\alpha]_{\text{D}}^{25} = -21.1^\circ$ (C = 0.53 in MeOH);
 NMR (CDCl_3): 1.18-1.90 (19H, m, αCH_3 and
 decahydronaphthyl x 16), 2.88-3.42 (4H, m, 2 x CH_2),

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4.05-4.20 (1H, m, α CH), 4.45-4.55 and 4.65-4.80 (1H, 2 x m, CHO), 4.96, 5.04 (1H, 2 x broad s, urethane), 5.29, 6.45 (2H, 2 x broad s, NH₂), 5.95, 6.21 (1H, 2 x s amide NH), 7.01 (2H, m, aromatics), 7.16-7.33 (8H, m, aromatics);

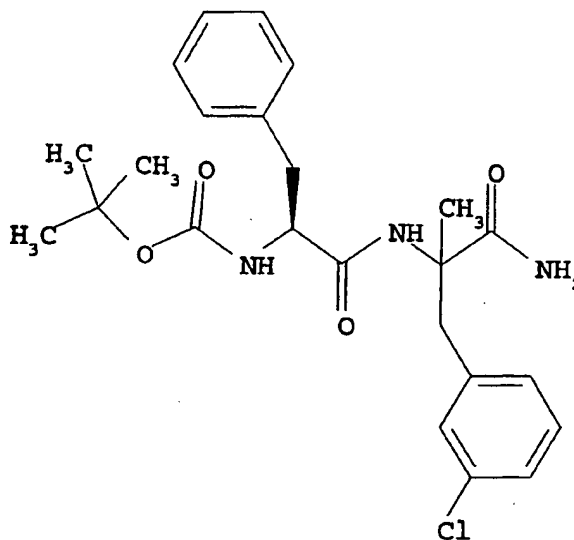
Analysis calculated for C₃₀H₃₉N₃O₄:

C, 71.26; H, 7.77; N, 8.31.

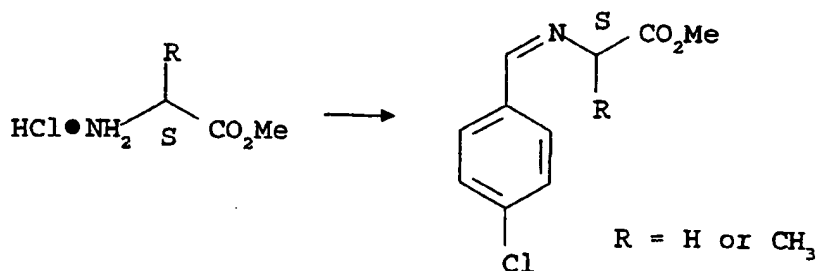
Found: C, 71.16; H, 7.78; N, 8.23.

EXAMPLE 20

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-3-chloro- α -methyl-



Step 1



R = Me

To a suspension of S-alanine methyl ester hydrochloride (5 g, 35.8 mmol), magnesium sulphate

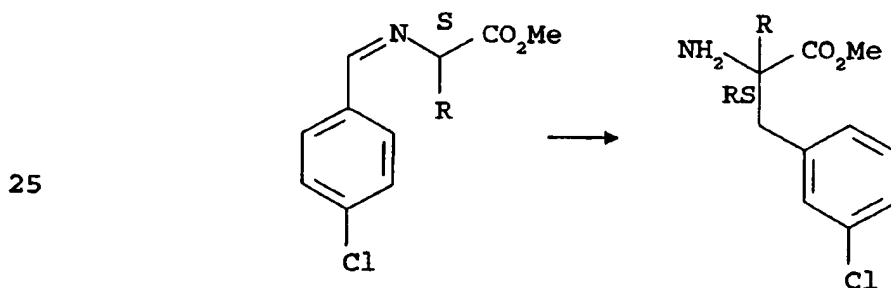
-94-

(0.75 g) and 4-chlorobenzaldehyde (5.035 g, 35.8 mmol) in dichloromethane (50 mL) was added triethylamine (3.64 g, 36.0 mmol). The reaction mixture was stirred overnight, filtered, and concentrated under reduced pressure. The residue was taken up in diethyl ether and the suspension filtered. The filtrate was concentrated under reduced pressure to yield the desired product (8.0 g, 99%) as a colorless oil; NMR 1.52 (3H, d, $J = 6.8$ Hz, $\text{CH}-\text{CH}_3$), 3.75 (3H, s, OCH_3), 4.16 (1H, q, $J = 6.8$ Hz, $\text{CH}-\text{CH}_3$), 7.38 (2H, d, $J = 8.5$ Hz, aromatics), 7.71 (2H, d, $J = 8.5$ Hz, aromatics), 8.26 (1H, s, Ar-CH = N).

R = H

The R = H analog was prepared by the same method. NMR: 3.78 (3H, s, OCH_3), 4.41 (2H, s, NCH_2CO), 7.40 (2H, d, $J = 8.4$ Hz, aromatics), 7.72 (2H, d, $J = 8.4$ Hz, aromatics), 8.26 (1H, s, Ar CH = N).

Step 2

R = H or CH_3

To a solution of the Schiff base (prepared, Example 20, Step 1) (0.5 g, 2.2 mmol) in tetrahydrofuran (10 mL) at -78°C was added LHMDS (2.43 mL of 1 M, 2.4 mmol). The mixture was stirred at -78°C for 0.5 hour and the 3-chlorobenzyl bromide (0.455 g, 2.2 mmol) added. The reaction was allowed to slowly warm to room temperature over 4 hours, 1 M HCl

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solution (10 mL) was added and the reaction stirred at room temperature for 20 hours. The reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was made basic with sodium bicarbonate and extracted with ethyl acetate. The organic extracts were dried over magnesium sulphate and evaporated to yield the product, 0.24 g (48%) as a yellow oil.

IR (film): 2951 (CH) and 1735 (ester C = O);

NMR (CDCl₃): 1.37 (3H, s, αCH₃), 2.76, 3.07 (2H, 2 × d, J = 14 Hz, CH₂), 3.74 (3H, s, OCH₃), 6.98-7.08 (1H, m, aromatics), 7.15-7.25 (3H, m, aromatics).

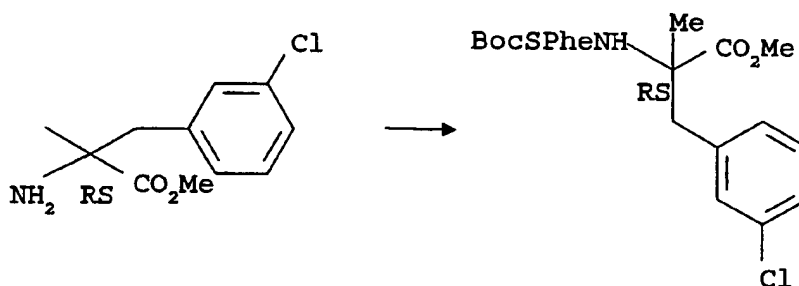
The analog in which R = H was prepared by the same procedure, 368 mg, 41% yield;

IR (film): 2951 and 1737 cm⁻¹;

M/e (CI): 214 (M+1) and 154 (100%);

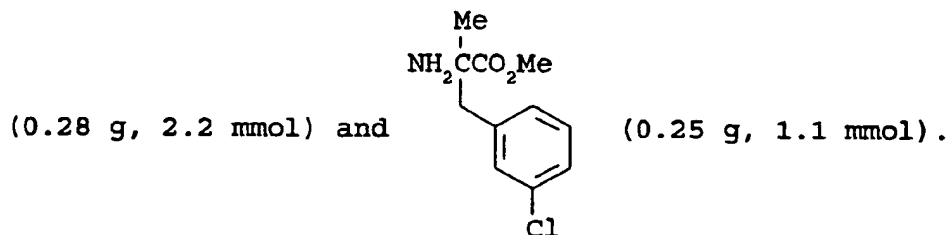
NMR DMSO-d₆: δ 1.87 (2H, bs, -NH₂), 2.75 (1/2 × 2H, 1/2 × ABX, J = 13.4 Hz, 7.7 Hz) and 2.88 (1/2 × 2H, 1/2 × ABX, J = 13.4 Hz, 5.9 Hz, benzyl CH₂-), 3.58 (4H, m, -CO₂CH₃, αH), 7.13-7.33 (4H, m, Ar).

Step 3



To a stirred solution of Boc-S-phenylalanine (0.29 g, 1.1 mmol) in dimethylformamide (5 mL) was added HBTU (0.42 g, 1.1 mmol), diisopropylamine

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The reaction was stirred at room temperature for 20 hours. The dimethylformamide was removed in vacuo and the residue taken up in ethyl acetate, washed with 0.1 hydrochloric acid, dried over magnesium sulphate and the solvent removed in vacuo. Purification by column chromatography gave a white amorphous solid, 0.34 g (65%), mp 38-42°C;

IR (film): 3308 (NH), 2980 (CH), 1738 (C = O, ester), 1661 (amide I, overlapping urethane, C = O), and 1519 (amide II);

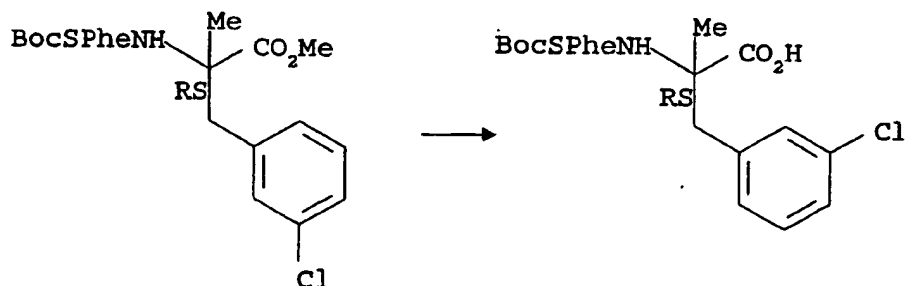
NMR (CDCl₃): 1.36, 1.39 (9H, 2 × s, (CH₃)₃C), 1.54, 1.57 (3H, 2 × s, αCH₃), 2.90-3.52 (4H, m, 2 × βCH₂), 3.73, 3.74 (3H, 2 × s, OCH₃), 4.20-4.32 (1H, m, αCH), 4.85-4.95 (1H, m, urethane NH), 6.41, 6.50 (1H, 2 × s, amide NH), 6.75-6.85 (1H, m, aromatic), 6.96-6.99 (1H, m, aromatic) 7.08-7.30 (7H, m, aromatics);

Analysis calculated for C₂₅H₃₁ClN₂O₅:

C, 63.22; H, 6.58; N, 5.90.

Found: C, 63.05; H, 6.53; N, 5.84.

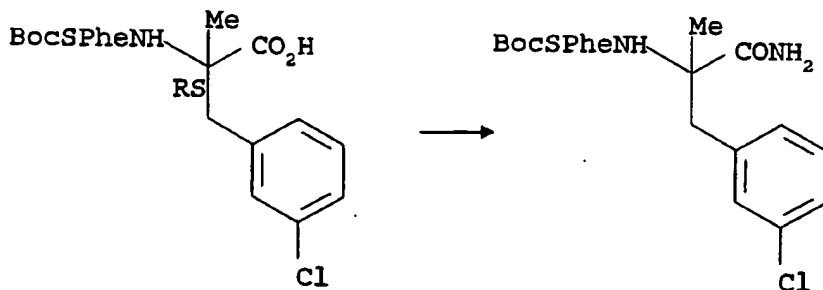
-97-

Step 4

To a stirred solution of the ester (0.30 g, 0.63 mmol) in tetrahydrofuran (8 mL)/water (2 mL) was added lithium hydroxide (0.02 g, 0.83 mmol). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure. The residue was partitioned between ethyl acetate and 0.1 M hydrochloric acid. The organic layer was dried over magnesium sulphate and evaporated to yield the desired acid as a crude sample (0.14 g, 48%);

IR (film): 3340 (NH), 2980 (CH), 1713 (C = O acid), 1662 (amide I), and 1514 (amide II);

20 NMR (CDCl₃): 1.32, 1.39 (9H, 2 × s, (CH₃)₃C), 1.53 (3H, s, αCH₃), 2.85-3.55 (4H, m, 2 × βCH₂), 4.60-4.75 (1H, m, αCH), 5.15-5.45 (1H, m, urethane NH), 6.80-7.29 (10H, m, 9 × aromatics, amide NH).

Step 5

To a stirred solution of the acid (0.221 g, 0.48 mmol) in ethyl acetate (10 mL) was added HOBt

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(0.078 g, 0.48 mmol) and DCC (0.099 g, 0.48 mmol). The reaction mixture was filtered after 3 hours and aqueous ammonia (0.205 g) added to the filtrate. After stirring for 3 days, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by column chromatography to yield the product, 0.16 g (73%) as a white crystalline solid, mp 142-148°C;

IR (film): 3308 (NH), 2980 (CH), 1667 (amide I), and 1498 (amide II);

NMR (CDCl₃): 1.34, 1.36 (9H, 2 × s, (CH₃)₃C), 1.54, 1.61 (3H, 2 × s, αCH₃), 2.79-3.52 (4H, m, βCH₂ × 2), 4.04-4.15 (1H, m, αH), 4.89-4.94 (1H, m, urethane NH), 5.18-5.32 (1H, m, NH₂), 6.01, 6.17 (1H, 2 × s, NH), 6.55-6.80 (1H, m, NH₂), 6.89-7.34 (9H, m, aromatics);

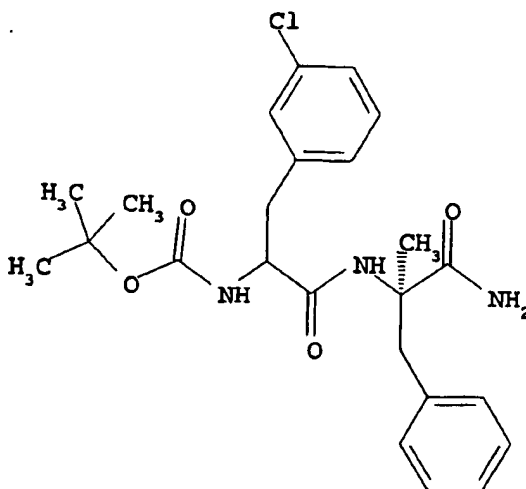
Analysis calculated for C₂₄H₃₀ClN₃O₄:

C, 62.67; H, 6.60; N, 9.14.

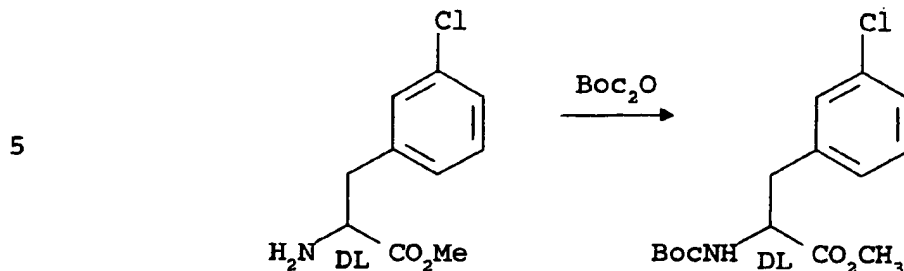
Found: C, 62.81; H, 6.57; N, 9.11.

EXAMPLE 21

D-Phenylalaninamide, 3-chloro-N-[(1,1-dimethylethoxy)-carbonyl]-DL-phenylalanyl-α-methyl-



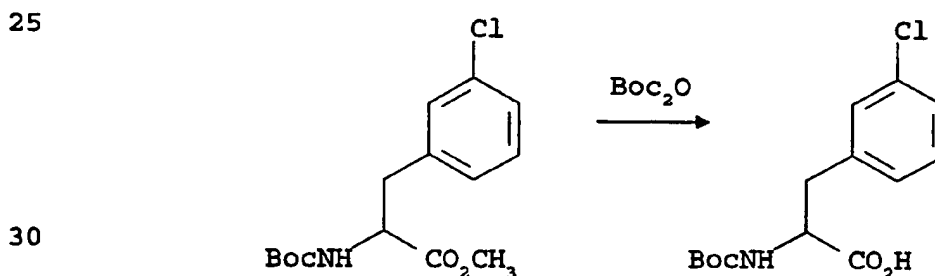
-99-

Step 1

10 3-Chlorophenylalanine (0.350 g, 1.64 mmol), di-tert-butyl dicarbonate (0.395 g, 1.80 mmol), 10% Na_2CO_3 (aqueous) solution (5 mL), and dioxan (15 mL) were stirred together at room temperature for 6.5 hours. The mixture was then evaporated to dryness and the residue was partitioned between ethyl acetate and water. The organic phase was washed with 10% citric acid solution and water. Drying (MgSO_4) and evaporation gave a yellow oil (0.390 g, 76%);

15 IR (film): 3362, 2978, 1744, and 1716 cm^{-1} ; M/e (CI): 314 (M+1) and 214 (100%);

20 NMR (DMSO-d_6): δ 1.31 (9H, s, Boc), 2.78-3.08 (2H, m, benzyl- CH_2 -), 3.62 (3H, s, $-\text{CO}_2\text{CH}_3$), 4.19 (1H, m, αH), 7.18-7.38 (5H, m, Ar, $-\text{OCONH}-$).

Step 2

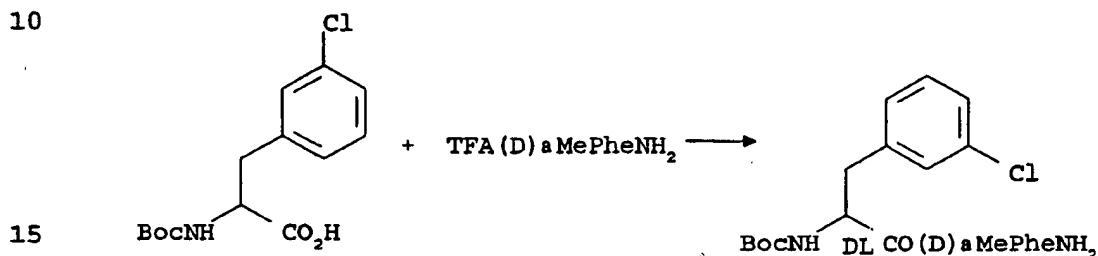
35 Boc-3-chlorophenylalaninemethyl ester (379 mg, 1.2 mmol) was dissolved in dioxan (10 mL). 1 M LiOH (aqueous) (2.4 mL, 2.4 mmol) was added dropwise and the mixture was stirred at room temperature for 2 days. On evaporation of the solvents, the residue was

-100-

partitioned between water and ethyl acetate. The aqueous layer was acidified to ~pH 4 with citric acid and extracted with ethyl acetate. Drying (MgSO_4) and evaporation gave a yellow oil (294 mg, 82%);

5 NMR (DMSO-d_6): δ 1.31 (9H, s, Boc), 2.75-3.10 (2H, m, benzyl- CH_2 -), 4.10 (1H, m, αH), 7.10-7.38 (5H, m, Ar, - CONH-), 12.60 (1H, bs, - CO_2H).

Step 3



Boc(DL)-3-chlorophenylalanine (0.180 g, 0.6 mmol), HBTU (0.227 g, 0.6 mmol), and diisopropylethylamine (0.311 mL, 0.6 mmol) were stirred in DMF (5 mL) for 20 minutes. TFA·(D) $\alpha\text{MePheNH}_2$ (0.175 g, 0.6 mmol) in DMF (3 mL) was added and the resulting solution was stirred for 15 hours at room temperature. On removal of the DMF, the residue was partitioned between water and ethyl acetate. The organic phase was washed with 10% citric acid solution, 10% Na_2CO_3 solution, and water. Drying (MgSO_4) gave a white solid which was further purified by reverse phase column chromatography using 60% to 90% $\text{MeOH}/\text{H}_2\text{O}$ over 40 minutes, yielding a white solid (0.145 g, 52%);

30 IR (film): 3306 and 1667 cm^{-1} ;

MS (CI): 460 ($\text{M}+1$) and 134 (100%);

NMR (DMSO-d_6): δ 1.28 ($1/2 \times 9\text{H}$, s) and δ 1.29

($1/2 \times 9\text{H}$, s, Boc), 1.35 ($1/2 \times 3\text{H}$, s) and 1.38

($1/2 \times 3\text{H}$, s, αCH_3), 2.65-3.37 (4H, m, $\beta\text{-CH}_2$ -s), 4.04

35 ($1/2 \times 1\text{H}$, m) and 4.13 ($1/2 \times 1\text{H}$, m, αH), 7.05-7.37

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(12H, m, Ar, -CONH₂, -OCONH-), 7.78 (1/2 × 1H, s) and 7.80 (1/2 × 1H, s, -CONH-);

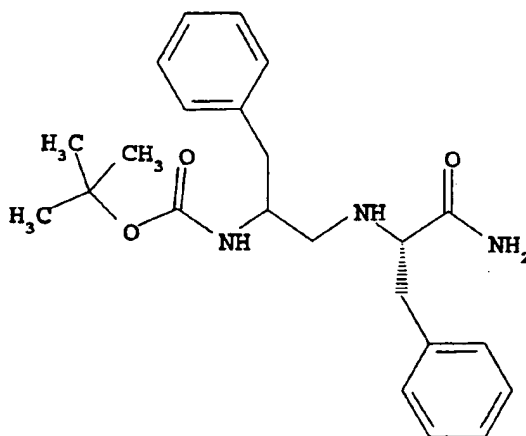
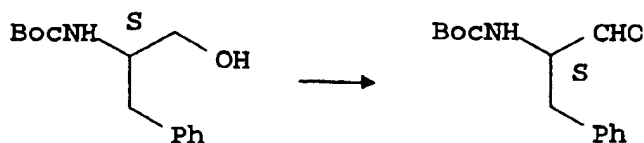
Analysis calculated for C₂₄H₃₀N₃O₄Cl:

C, 62.67; H, 6.57; N, 9.14.

5 Found: C, 62.50; H, 6.61; N, 8.96.

EXAMPLE 22

10 Carbamic acid, [2-[[2-amino-2-oxo-1-(phenylmethyl)-ethyl]amino]-1-(phenylmethyl)ethyl]-, 1,1-dimethylethyl ester

Step 1

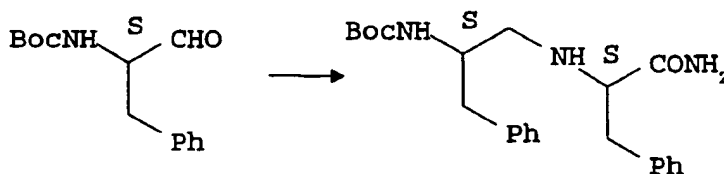
30 DMSO (0.340 g, 4.35 mmol) in CH₂Cl₂ (3 mL) was added to a solution of oxalyl chloride (0.275 g, 2.17 mmol) in CH₂Cl₂ (10 mL) cooled to -60°C. The cold mixture was stirred for 20 minutes and then the alcohol (0.500 g, 2.00 mmol) in CH₂Cl₂ (3 mL) was added. The reaction was again stirred at -60°C for 20 minutes
35 followed by addition of Et₃N (0.611 g, 6.04 mmol) in CH₂Cl₂ (3 mL). The reaction was allowed to warm to

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room temperature overnight and then the solvent removed in vacuo. The residue was dissolved in EtOAc and washed with 0.5 M HCl, the EtOAc layer dried over MgSO_4 , filtered, and the solvent removed in vacuo. The residual product was purified by chromatography on silica using 25% EtOAc/75% n-hexane as eluant to give the aldehyde as a white solid (0.158 g, 32%);

IR (film): 3365, 2969, 1732, 1688, and 1520 cm^{-1} ;

NMR (CDCl_3): δ 1.40 (9H, s, $\text{C}(\text{CH}_3)_3$), 3.11 (2H, d, $J = 6.0\text{ Hz}$, PhCH_2), 4.41 (1H, m, CH_2CHCHO), 5.02 (1H, brs, NHCO), 7.16 (2H, d, $J = 7.0\text{ Hz}$, Ph), 7.25 (3H, m, Ph), 9.65 (1H, s, CHO).

Step 2

Sodium cyanoborohydride (0.6 mL of 1 M solution in THF, 0.60 mmol) was added to a solution of the aldehyde (0.150 g, 0.60 mmol) and S-phenylalaninamide (0.098 g, 0.60 mmol) in MeOH/AcOH (5 mL, 99:1 mixture). The reaction mixture was stirred at room temperature for 6 hours and then saturated NaHCO_3 solution added and the mixture extracted into EtOAc. The EtOAc solution was dried over MgSO_4 , filtered, and the solvent removed in vacuo. The crude product was purified by chromatography on silica using 75% EtOAc/25% n-hexane as eluant giving the aminomethylene compound as an off-white solid (0.075 g, 31%), mp $97-100^\circ\text{C}$;

IR (film): 3358, 2980, 1683, 1660, 1604, 1525, and 1170 cm^{-1} ;

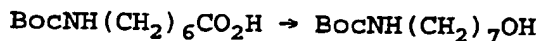
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NMR (CDCl₃): δ 1.39 (9H, s, C(CH₃)₃), 2.40-2.80 (6H, m, PhCH₂, CH₂NH, CH₂NHCH₂, CH₂CHNHCOO), 3.20 (2H, m, PhCH₂CHCONH₂), 3.80 (1H, m, HNCHCONH₂), 4.55 (1H, m, NHCOO), 6.25 (1H, bs, CONHH), 6.90-7.30 (11H, m, CONHH, 2C₆H₅);

Analysis calculated for C₂₃H₃₁N₃O₃·0.20CHCl₃.

EXAMPLE 23

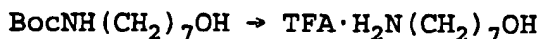
D-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl-N-[7-[(aminocarbonyl)amino]heptyl]- α -
methyl-

Step 1

BocNH(CH₂)₆CO₂H (0.45 g, 1.8 mmol) and N-methyl-morpholine (0.22 mL, 2 mmol) were dissolved in THF (10 mL). The solution was cooled to 0°C and ethylchloroformate (0.19 mL, 2 mmol) in THF (10 mL) was added dropwise over 10 minutes. The solution was stirred for 1 hour, and the precipitate was removed by filtration. The filtrate was cooled on an ice bath and LiBH₄ (3 mL, 2 M in THF, 6 mmol) was added dropwise over 5 minutes. The mixture was stirred with slow warming to room temperature over 3 hours. The solvent was removed in vacuo, and the residue was redissolved in EtOAc (50 mL). The organic was washed with water (3 x 50 mL), brine (50 mL), and then dried over MgSO₄. Removal of the solvent in vacuo gave a clear oil 0.402 g, 90%.

IR (film): 3344, 2931, 2858, 1689, and 1531 cm⁻¹.
 NMR (CDCl₃): 1.28-1.60 (19H, m, BocCH₃ x 3, CH₂ x 5), 3.10 (2H, m, CONHCH₂), 3.64 (2H, m, CH₂OH), 4.50 (1H, br s, urethane NH).

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Step 2

5 BocNH(CH₂)₇OH (0.40 g, 1.7 mmol) was dissolved in a 50:50 TFA/DCM solution (20 mL). The reaction mixture was stirred for 1 hour after which the solvent was removed in vacuo. The residue was azeotroped with toluene (5 x 10 mL), and the resulting oil was used without purification.

10 Step 3

15 BocSPheRαMePheOH (0.64 g, 1.5 mmol), DCC (0.31 g, 1.5 mmol), and HOBT (0.20 g, 1.5 mmol) were dissolved in DMF (3 mL). The solution was stirred for 5 minutes after which TFA·H₂N(CH₂)₇OH (0.66 g, 1.7 mmol) and DIPEA (0.7 mL, 4 mmol) were added. The solution was stirred for 15 hours, and the precipitate then removed by filtration. The solvent was removed in vacuo and the residue was dissolved in EtOAc (100 mL). The organic was washed with 1 M HCl (3 x 50 mL), saturated NaHCO₃ (3 x 50 mL), water (3 x 50 mL), and brine (50 mL). The organic was dried over MgSO₄ and the solvent was concentrated in vacuo. The residue was purified by reverse phase chromatography 0% to 100% MeOH/H₂O over 30 minutes. Removal of the solvent gave a white foam 0.54 g, 67%, mp 46-49°C.

IR (film): 3324, 3029, 2929, 1661, and 1516 cm⁻¹.

20 NMR (CDCl₃): δ 1.29-1.58 (22H, m, BocCH₃ x 3, αCH₃, CH₂ x 5), 2.75-3.45 (6H, m, βCH₂ x 2, CONHCH₂),
30 3.63 (2H, t, J = 6.8 Hz, CH₂OH), 4.00 (1H, m, αCH), 4.96 (1H, br d, urethane NH), 5.85 (1H, br s, amide NH), 6.65 (1H, br s, amide NH), 6.96-6.98 (2H, m, aromatics), 7.19-7.35 (8H, m, aromatics).

MS (CI): 540 (m⁺), 440, 134.

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Analysis calculated for $C_{31}H_{45}N_3O_5 \cdot 1/4H_2O$:

C, 68.42; H, 8.43; N, 7.72

Found: C, 68.46; H, 8.32; N, 7.69.

5 Item 4

BocSPheRoMePheNH(CH₂)₇OH → BocSPheRoMePheNH(CH₂)₇OTOS

10 BocSPheRoMePheNH(CH₂)₇OH (267 mg, 0.5 mmol) was dissolved in DCM (3 ml). Tosyl chloride (105 mg, 0.55 mmol), triethylamine (84 μL, 0.6 mmol), and DMAP (catalytic) were added and the reaction mixture was stirred overnight. The solution was diluted with DCM (50 mL) and washed with 1 M HC (3 × 20 mL), saturated NaHCO₃ (3 × 20 mL), H₂O (3 × 20 mL), and brine (20 mL). The organic was dried over MgSO₄ and the solvent was removed in vacuo. A white foam (359 mg) was obtained and was used without purification.

15 IR (film): 3351, 2978, 2935, 1687, 1657, 1521, 1598, 1366, and 1175 cm⁻¹.

20 NMR (CDCl₃): δ 1.21-1.66 (22H, m, CH₃ × 3), αCH₃, CH₂ × 5), 2.45 (3H, s, CH₃), 2.75-3.45 (6H, m, βCH₂ × 2, CONHCH₂), 4.01 (3H, m, αCH, CH₂OTOS), 4.90 (1H, br d, urethane NH), 5.85 (1H, br s, amide NH), 6.70 (1H, br s, amide NH), 6.96-6.98 (2H, m, aromatics), 7.12-7.35 (10H, m, aromatics), 7.79 (2H, d, J = 8.4 Hz, aromatics).

25 Step 5

BocSPheRoMePheNH(CH₂)OTOS → BocSPheRoMePheNH(CH₂)₇N₃

30 BocSPheRoMePheNH(CH₂)₇OTOS (317 mg, 0.46 mmol) was dissolved in DMF (5 mL) and NaN₃ (33 mg, 0.51 mmol) was added. The reaction mixture was heated to 60°C for 3 hours, then allowed to cool to room temperature and stirred overnight. The solution was poured onto ice and the aqueous was extracted with DCM (3 × 100 mL). The combined extracts were washed with water (3 × 100 mL), brine (100 mL), and dried over MgSO₄. The

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solvent was removed in vacuo and the resulting residue was purified by column chromatography, 50% to 70% ether in hexane. A white foam was obtained 179 mg, 69%.

IR (film): 3322, 2932, 2095, 1683, 1651, and 1517 cm^{-1} .

NMR (CDCl_3): δ 1.30-1.60 (22H, m, $\text{BocCH}_3 \times 3$, αCH_3 , $\text{CH}_2 \times 5$), 2.75-3.45 (8H, m, $\beta\text{CH}_2 \times 2$, CONHCH_2 , CH_2N_3), 4.00 (1H, m, αCH), 4.90 (1H, br s, urethane NH), 5.85 (1H, br s, amide NH), 6.70 (1H, br s, amide NH), 6.97-6.99 (2H, m, aromatics), 7.10-7.36 (8H, m, aromatics).

Step 6

$\text{BocSPheR}\alpha\text{MePhenNH}(\text{CH}_2)_7\text{N}_3 \rightarrow \text{BocSPheR}\alpha\text{MePhenNH}(\text{CH}_2)_7\text{NH}_2 \cdot \text{HCl}$

$\text{BocSPheR}\alpha\text{MePhenNH}(\text{CH}_2)_7\text{N}_3$ (275 mg, 0.49 mmol), was dissolved in ethanol (20 mL) and Lindlar catalyst (60 mg) was added. The solution was hydrogenated at 40 psi, 30°C for 6 hours, after which the catalysts was removed by filtration through Kieselguhr. The solvent was removed in vacuo to give a white foam 266 mg. The product was dissolved in MeOH/1 M HCl and purified on a reverse phase column, 50% to 100% MeOH/ H_2O . Removal of the solvent gave a white solid 215 mg, 76%, mp 94-102°C.

IR (film): 3322, 2933, 1689, 1652, and 1520 cm^{-1} .

NMR (CDCl_3): δ 1.20-1.50 (20H, m, $\text{BocCH}_3 \times 3$, αCH_3 , $\text{CH}_2 \times 4$), 2.84 (2H, br t, $\text{CH}_2\text{CH}_2\text{NH}_2$), 2.75-3.33 (8H, m, $\beta\text{CH}_2 \times 2$, CONHCH_2 , CH_2NH_2), 4.08 (1H, m, αCH), 5.20 (1H, br s, urethane NH), 6.24 (1H, br s, amide NH), 6.79 (1H, brt, amide NH), 7.00 (2H, m, aromatics), 7.18-7.33 (8H, m, aromatics), 8.34 (3H, br s, NH_3^+Cl^-).

Analysis calculated for $\text{C}_{31}\text{H}_{46}\text{N}_4\text{O}_4 \cdot 1.3 \text{ HCl}$:

C, 63.53; H, 8.13; N, 9.56.

Found: C, 63.43; H, 8.10; N, 9.51.

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Step 7

5 $\text{BocSPheRoMePheNH}(\text{CH}_2)_7\text{NH}_2 \cdot \text{HCl}$ (130 mg, 0.24 mmol)
 and triethylamine (33 μL , 0.24 mmol) were dissolved in
 THF (3 mL). Trimethylsilylisocyanate (67 μL , 0.5 mmol)
 was added and the reaction mixture was stirred
 overnight. The solvent was removed in vacuo and the
 residue was redissolved in EtOAc (100 mL). The
 10 solution was washed with 1 M HCl (3 \times 50 mL), saturated
 NaHCO_3 (3 \times 50 mL), and water (3 \times 50 mL). The organic
 was dried over MgSO_4 and the solvent was removed
 in vacuo. The residue was purified by column
 chromatography, 5% MeOH/DCM to give a white foam 66 mg,
 15 47%, mp 65-72°C.

IR (film): 3344, 2931, 1693, 1651, and 1539 cm^{-1} .

NMR (CDCl_3): δ 1.21-1.52 (22H, m, $\text{BocCH}_3 \times 3$, αCH_3 ,
 $\text{CH}_2 \times 5$), 2.75-3.22 (8H, m, $\beta\text{CH}_2 \times 2$, CONHCH_2 ,
 $\text{CH}_2\text{NHCONH}_2$), 4.02 (1H, m, αCH), 4.55 (2H, br s,
 20 NHCONH_2), 5.05, 5.15 (2H, 2 \times br s, urethane NH,
 $\text{CH}_2\text{NHCONH}_2$), 5.95 (1H, br s, amide NH), 6.80 (1H, br s,
 amide NH), 6.97-6.99 (2H, m, aromatics), 7.18-7.34 (8H,
 m, aromatics).

MS (FAB): 605 (M^+Na), 582 (M^+H), 482, 335.

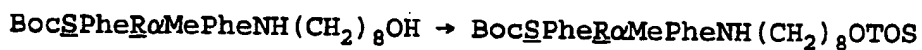
25 Analysis calculated for $\text{C}_{31}\text{H}_{47}\text{N}_5\text{O}_5 \cdot 0.4 \text{ H}_2\text{O}$:

C, 65.26; H, 8.04; N, 11.89.

Found: C, 65.32; H, 8.07; N, 11.79.

EXAMPLE 24

30 D-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-
L-phenylalanyl- α -methyl-N-[8-(methylsulfonyl)octyl]
Step 1



35 $\text{BocSPheRoMePheNH}(\text{CH}_2)_8\text{OH}$ (Example 1) (0.200 g,
 0.36 mmol) and triethylamine (60 μL , 0.43 mmol) were
 dissolved in DCM (2 mL). Tosyl chloride (0.076 g,

-108-

0.4 mmol) and DMAP (catalytic) were then added and the solution was stirred for 15 hours. The reaction mixture was diluted with CDM (50 mL), then washed with 2 M HCl (3 x 30 mL), saturated NaHCO₃ (3 x 50 mL), and water (3 x 30 mL). The organic was dried over MgSO₄, filtered, and the solvent was removed in vacuo. The residue was purified by column chromatography, 3% MeOH in DCM to give an oil 0.179 g, 70%.

IR (film): 3353, 2932, 2862, 1690, 1656, and 1521 cm⁻¹.

NMR (CDCl₃): δ 1.65-1.98 (24H, m, BocCH₃ x 3, α CH₃, CH₂ x 2), 2.45 (3H, s, TOSCH₃), 2.74-3.48 (6H, m, β CH₂ x 2, CONHCH₂), 4.01 (3H, m, α CH, CH₂OTOS), 4.90 (1H, br d, urethane NH), 5.82 (1H, br s, amide NH), 6.70 (1H, br, amide NH), 6.95-6.98 (2H, m, aromatics), 7.19-7.36 (10H, m, aromatics), 7.78 (2H, d, J = 8.4 Hz, aromatics).

Step 2

BocSPheR α MePheNH(CH₂)₈OTOS \rightarrow BocSPheR α MePheNH(CH₂)₈SCH₃
 BocSPheR α MePheNH(CH₂)₈OTOS (0.17 g, 0.24 mmol) and K₂CO₃ (0.05 g, 0.36 mmol) were dissolved in DMF (3 mL). Methane thiol was bubbled through the solution for 10 minutes and stirring was continued for a further 2.5 hours. The reaction mixture was then diluted with ether (50 mL) and washed with brine (3 x 30 mL). The organic was dried over MgSO₄, filtered, and the solvent was removed in vacuo to give a clear glass 0.113 g, 81%.

IR (film): 3326, 2928, 2855, 1686, 1652, and 1517 cm⁻¹.

NMR (CDCl₃): δ 1.22-1.62 (24H, m, BocCH₃ x 3, α CH₃, CH₂ x 6), 2.09 (3H, s, SCH₃), 2.48 (2H, t, CH₂SCH₃), 2.75-3.42 (6H, m, β CH₂ x 2, CONHCH₂), 4.00 (1H, m, α CH), 4.90 (1H, br s, urethane NH), 5.85 (1H, br s,

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amide NH), 6.62 (1H, br s, amide NH), 6.96-6.98 (2H, m, aromatics), 7.19-7.35 (8H, m, aromatics).

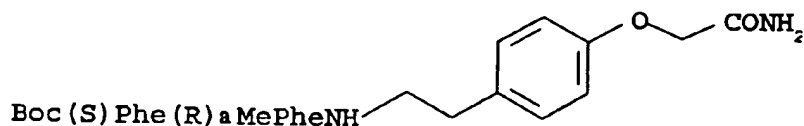
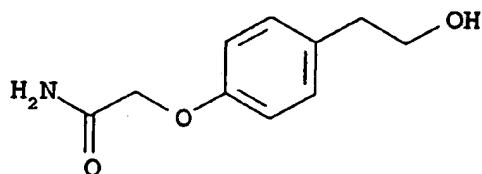
Step 3

- 5 $\text{BocSPheR}\alpha\text{MePhenNH(CH}_2)_8\text{SCH}_3 \rightarrow \text{BocSPheR}\alpha\text{MePhenNH(CH}_2)_8\text{SO}_2\text{CH}_3$
 $\text{BocSPheR}\alpha\text{MePhenNH(CH}_2)_8\text{SCH}_3$ (0.113 g, 0.2 mmol),
was dissolved in DCM (10 mL) and the solution was
cooled to 0°C on an ice bath. MCPBA (0.104 g,
0.6 mmol) was added and the solution was stirred at 0°C
10 for 1 hour. The reaction was allowed to warm to room
temperature and stirring was continued for a further
6 hours. The solution was diluted with DCM (30 mL) and
washed with saturated NaHCO_3 (3 x 30 mL), 10% Na_2SO_5
(3 x 30 mL), and water (2 x 30 mL). The organic was
15 dried over MgSO_4 , filtered, and the solvent was
concentrated in vacuo. The residue was purified by
column chromatography 50% to 80% EtOAc in hexane to
give a white solid 0.084 g, 68%, mp 51-56°C.
 $[\alpha]_D^{21} +13$ (C=0.8 in CH_3OH)
20 IR (film): 3350, 2931, 2857, 1690, 1655, and
1520 cm^{-1} .
 NMR (CDCl_3): 1.21-1.46 (22H, m, $\text{BocCH}_3 \times 3$, αCH_3 ,
 $\text{CH}_2 \times 5$), 1.84 (2H, m, $\text{CH}_2\text{CH}_2\text{SO}_2\text{CH}_3$), 2.77-3.45 (8H, m,
 $\beta\text{CH}_2 \times 2$, CONHCH_2 , $\text{CH}_2\text{SO}_2\text{CH}_3$), 2.89 (3H, s, SO_2CH_3),
25 4.00 (1H, m, αCH), 4.90 (1H, br, urethane NH), 5.85
(1H, br s, amide NH), 6.70 (1H, br, amide NH), 6.97
(2H, m, aromatics), 7.19-7.37 (8H, m, aromatics).
 MS (FAB, thioglycerol): 1232.2 (M^{2+}), 616.3 (MH^+),
516.2, 369, 325, 281.
30 Analysis calculated for $\text{C}_{33}\text{H}_{49}\text{N}_3\text{O}_6\text{S} \cdot 0.3 \text{ H}_2\text{O}$:
 C, 63.80; H, 8.05; N, 6.76.
 Found: C, 63.75; H, 7.96; N, 6.68.

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EXAMPLE 25

(1-(1-[2-(4-Carbamoylmethoxy-phenyl)-ethylcarbamoyl]-
1-methyl-2-phenyl-ethylcarbamoyl)-2-phenyl-ethyl)-
carbamic acid tert-butyl ester

Step 1

15 Potassium carbonate (1.20 g, 8.7 mmol) was added to a solution of 4-hydroxyphenethyl alcohol (1.32 g, 8.7 mmol) and 2-bromoacetamide (1.32 g, 8.7 mmol) in butan-2-one (25 mL). The suspension was heated at reflux for 4 hours and stirred at room temperature for 15 hours. The suspension was filtered and evaporated down to an off-white solid. Further purification by column chromatography using 5% MeOH/EtOAc gave a white solid (1.18 g, 92%).

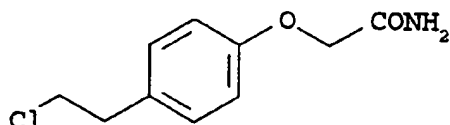
25 NMR (DMSO-d₆): δ 2.60 (2H, t, -CH₂Ar), 3.49 (2H, m, -CH₂OH), 4.32 (2H, s, -CH₂-CONH₂), 4.54 (1H, bs, -OH), 6.79 (2H, d, Ar), 7.07 (2H, d, Ar), 7.31 (1H, bs), and 7.42 (1H, bs, -CONH₂).

MS (CI): 178 (100%), 196 (M+1).

IR (film): 3395, 3177, 2927, 1639 cm⁻¹.

30

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Step 2

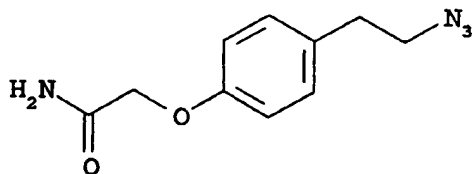
5

Tosyl chloride (1.29 g, 6.76 mmol) in DCM (25 mL) was added dropwise to a solution of the alcohol (1.10 g, 5.63 mmol) in pyridine. The suspension was stirred at room temperature for 16 hours. On removal of the solvents, the residue was taken up in DCM (100 mL) and extracted with 10% citric acid solution (3 x 100 mL) and water (2 x 80 mL). Drying (MgSO₄) and further purification by column chromatography using EtOAc:hexane (1:1) gave a white solid (400 mg, 33%).

NMR (DMSO-d₆): δ 2.91 (2H, t, J = 6 Hz, -CH₂-), 3.75 (2H, t, J = 6 Hz, -CH₂-), 4.34 (2H, s, -CH₂-), 6.83 (2H, d, Ar), 7.15 (2H, d, Ar), 7.32 (1H, bs), and 7.44 (1H, bs, -CONH₂).

MS (CI): 231 (M+1 \rightarrow NH₃; 100%), 233 (M+3+NH₂), 214 (M+1), 216 (M+1+2).

20

Step 3

25

The chloro compound (0.380 g, 1.78 mmol) was dissolved in DMF (20 mL). Sodium azide (0.127 g, 1.96 mmol) and sodium iodide (0.267 g, 1.78 mmol) were added and the mixture was heated to 90°C for 4 hours. On cooling, the mixture was poured onto 100 mL ice water and extracted with ether (3 x 100 mL). Drying and evaporation gave a white solid (0.35 g), 85% as the azide and 15% as chloro compound. Used crude in next step.

35

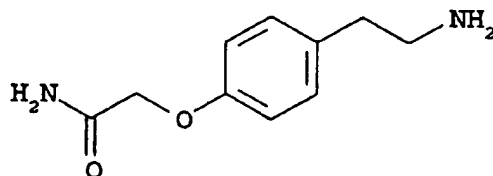
-112-

MS (CI): 164 (100%), 221 (M+1)

IR (film): .

Step 4

5



10

The crude azide (0.340 g, ~1.31 mmol) was dissolved in MeOH (30 mL) and Lindlar catalyst was added (0.170 g). This mixture underwent hydrogenation using the Parr apparatus at 43 psi and 25°C for 6 hours. The catalyst was removed by filtration through celite. Evaporation gave an oil which was triturated with ethyl acetate to form a white solid (0.220 g, 86%).

15

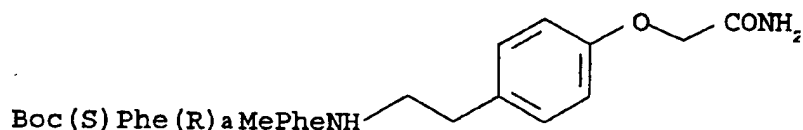
NMR (DMSO- d_6): 2.50-2.74 (4H, m, -CH₂-CH₂-), 4.32 (2H, s, -CH₂-), 6.83 (2H, m, Ar), 7.05 (2H, m, Ar), 7.32 (1H, bs), and 7.43 (1H, bs, -CONH₂).

20

MS (CI): 178 (100%), 195 (M+1).

Step 5

25



30

Dicyclohexylcarbodiimide (0.138 g, 0.67 mmol) in EtOAc (3 mL) was added dropwise to a solution of Boc(S)Phe(R)αMePhe-OH (0.285 g), and 1-hydroxybenzotriazole hydrate (0.090 g, 0.67 mmol) in ethyl acetate (20 mL). The resulting suspension was stirred for 1.5 hours and then cooled in the freezer. The mixture was filtered into a solution of the phenethylamine from Step 4 (0.130 g, 0.67 mmol) in DMF (5 mL) and ethyl acetate (5 mL) and allowed to stir at

35

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room temperature for 3 days. The solvents were removed under high vacuum and the residue was taken up in EtOAc (100 mL) and washed with 2 M HCl (2 x 100 mL), 10% sodium carbonate solution (2 x 70 mL), and water (70 mL). Further purification by reverse phase column chromatography using 60% to 80% MeOH/H₂O over 1 hour gave a white foam (0.165 g, 41%).

NMR (DMSO-d₆): δ 1.23 (3H, s, α CH₃), 1.26 (9H, s, Boc), 2.55-3.25 (8H, m, 2 x CH_2 -Ph, -CH₂-CH₂-), 4.13 (1H, m, α H), 4.31 (2H, s, -OCH₂-), 6.81-7.23 (15H, m, Ar, -OCONH-), 7.32 (1H, bs), and 7.42 (1H, bs, -CONH₂), 7.60 (1H, t, -CONH-), 7.76 (1H, s, -CONH-), mp 73-81°C. MS:

IR (film): 3321, 2932, 1694, 1669 cm⁻¹.

$[\alpha]_D^{23.3^\circ\text{C}} = +13.07$ (c=1.025; MeOH)

Analysis calculated for C₃₄H₄₂N₄O₆·0.35 H₂O

C, 67.05; H, 7.07; N, 9.20.

Found: C, 67.08; H, 7.12; N, 8.91.

EXAMPLE 26

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl- α -methyl-N-[9-(methylamino)-2-oxononyl]

Boc(S)Phe(R) α MePheNH(CH₂)₈CONHMe

The acid [Boc(S)Phe(R) α MePhe] (0.200 g; 0.34 mmol), HBTU (0.130 g; 0.34 mmol) and DIPEA (0.165 mL; 0.68 mmol) in DMF (8 mL) were stirred at room temperature for 20 minutes DIPEA (0.124 mL; 0.51 mmol) and methylamine hydrochloride (0.023 g; 0.34 mmol) were added and the mixture was stirred for 16 hours.

On removal of DMF, the residue was taken up in EtOAc (60 mL) and washed with 2 M HCl (2 x 50 mL), 10% Na₂CO₃ (2 x 50 mL) and brine (50 mL). Drying (MgSO₄) and further purification by column chromatography using 5% MeOH/DCM gave a white solid (0.204 g; 99%), mp 50-58°C;

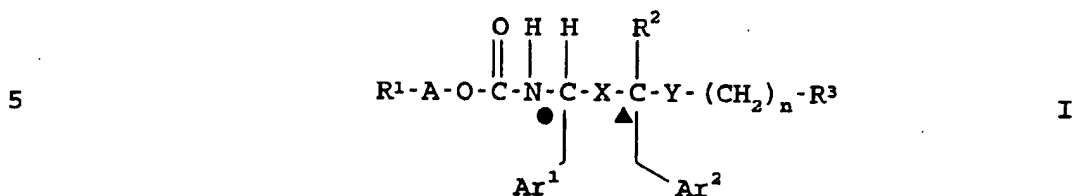
-114-

- NMR (CDCl₃): δ 1.22-1.64 (24H, m, Boc, α CH₃-(CH₂)₆-),
2.16 (2H, t, -CH₂C-), 2.78-2.90 (5H, m, N-Me, PhCHH-,
5 PhCHH-), 3.05-3.25 (3H, m, -CONHCH₂-, PhCHH-),
3.41 (1H, d, PhCHH-), 3.98-4.05 (1H, m, α H), 4.93 (1H,
d, -OCONH-), 5.62 (1H, bs, -CONHCH₃), 5.90 (1H, s,
-CONH-), 6.70 (1H, bs, -CONH-), 6.96-7.00 (2H, m, Ar),
7.18-7.40 (8H, m, Ar).
10 MS 495 (100%, m + 1)
IR (film): 3316, 2931, 1710, 1688, 1646 cm⁻¹
[α]_D^{21.9°C} = +10.14°C (C = 1.035; MeOH);
Analysis calculated for C₃₄H₅₀N₄O₅·0.3H₂O:
C, 68.04; H, 7.50; N, 9.33.
15 Found: C, 67.93; H, 7.47; N, 9.22.

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CLAIMS

1. A compound of formula



or a pharmaceutically acceptable salt thereof
 wherein:

R¹ is hydrogen,

OR⁴,

CO₂R⁴,

cyclo- or polycycloalkyl of from 4 to

10 carbons with from 0 to 3 substituents
 selected from:

alkyl,

halogen,

(CH₂)_mCO₂R⁴,

(CH₂)_mOR⁴ wherein m is an integer

of from 1 to 6 and R⁴ is

hydrogen or alkyl, or

phenyl unsubstituted or substituted by from

1 to 3 groups selected from:

alkyl,

halogen,

nitro,

CF₃,

(CH₂)_pOR⁶,

(CH₂)_pCO₂R⁶,

(CH₂)_pNR⁶R⁷ wherein p is an integer

of from 0 to 6 and R⁶ and R⁷

are each independently

hydrogen or alkyl;

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- 35 A is $-(\text{CH}_2)_q(\text{C}(\text{CH}_3)_2)_r(\text{CH}_2)_s-$ wherein q , r , and s
are integers of from 0 to 6, 0 to 1, and
0 to 6, respectively;
 Ar^1 and Ar^2 are each independently phenyl
unsubstituted or substituted with from
40 1 to 3 substituents selected from:
alkyl,
halogen,
nitro,
 CF_3 ,
45 $(\text{CH}_2)_t\text{OR}^6$,
 $(\text{CH}_2)_t\text{CO}_2\text{R}^6$, or
 $(\text{CH}_2)_t\text{NR}^6\text{R}^7$ wherein t is an integer of
from 0 to 6 and R^6 and R^7 are each
independently hydrogen or alkyl;
50 X and Y are each independently
-CONH-,
-CONCH₃-,
-COO-,
-CH₂NH-,
55 -NHCO-,
-CH₂O-,
-COCH₂-, or
-CH₂CH-;
 n is an integer of from 0 to 10; and
60 R^3 is hydrogen,
straight or branched alkyl of from 3 to
10 carbons with from 0 to 3 substituents
selected from:
 $(\text{CH}_2)_n\text{OR}^8$,
65 CO_2R^8 ,
-NHCOCH₃,
-NR⁸R⁹,
-SO₂Me,
-SOMe,
70 -SO₂NH₂,

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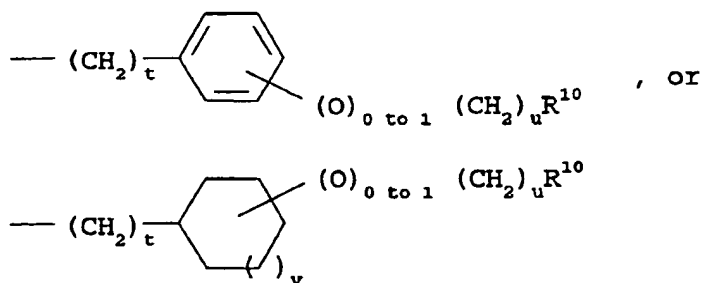
- CONR⁸R⁹,
- NHCONR⁸R⁹,
- COR⁴ wherein n is an integer of
from 0 to 6, R⁴ is as above,
R⁸ and R⁹ are each
independently hydrogen or
alkyl,
- guanidine,
- amidine,

75

80

R³ is also

85



90

wherein t is an integer of from 0 to 5,
v is an integer of from 0 to 2,
u is an integer of from 0 to 4, and
R¹⁰ is hydrogen, hydroxy, alkoxy,
COOH, CO₂alkyl, CONR⁸R⁹, NMCONR⁸R⁹
guanidine or amidine; and

95

• and ▲ indicate all stereoisomers.

2. A compound according to Claim 1 wherein:

R¹ is hydrogen,

OR⁴,

CO₂R⁴ wherein R⁴ is hydrogen, methyl, or
ethyl,

5

cycloalkyl of from 4 to 8 carbons,
bicycloalkyl of 10 carbons,
tricycloalkyl of 10 carbons, or
phenyl;

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10 A is $-(CH_2)_q(C(CH_3)_2)_r(CH_2)_s-$ wherein q, r, and s are integers of from 0 to 2, 0 to 1, and 0 to 4, respectively;

Ar¹ and Ar² are each independently phenyl unsubstituted or mono- or disubstituted by:

15 alkyl,
halogen,
CF₃,
NO₂, or
NH₂;

20 X and Y are each independently

-CONH-,
-CONCH₃-,
-CO₂-, or
-CH₂NH-;

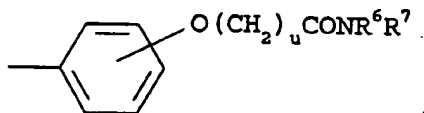
25 n is an integer of from 0 to 9; and

R³ is hydrogen,

straight, branched, or cyclic alkyl of from 3 to 10 carbons with from 0 to 3 substituents selected from:

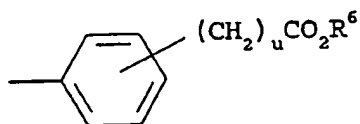
30 OH,
OCH₃,
CO₂R⁸,
NHCOCH₃,
NR⁸R⁹,
35 CONR⁸R⁹,
NHCONR⁸R⁹ wherein R⁸ and R⁹ are each independently selected from hydrogen and methyl, or
COCH₃,

40

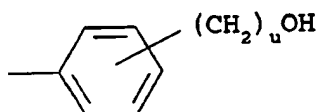


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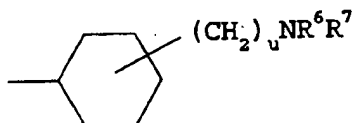


50



, or

55



60

wherein u is an integer of from 0 to 4 and R^6 and R^7 are each independently selected from hydrogen and methyl.

3. A compound according to Claim 1 wherein:

R^1 is hydrogen,

OR⁴,

CO₂R⁴ wherein R^4 is hydrogen or methyl,
cycloalkyl of from 5 to 7 carbons;

5

A is $-(CH_2)_q(C(CH_3)_2)_r(CH_2)_s-$ wherein q , r , and s are integers of from 0 to 3, 0 to 1, and zero, respectively;

Ar¹ and Ar² are each independently phenyl

10

unsubstituted or mono- or disubstituted by:

alkyl,

chloro, or

CF₃;

X and Y are each independently

15

-CONH-,

-CONCH₃-,

-CO₂-, or

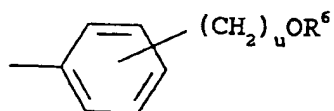
-CH₂NH-;

-120-

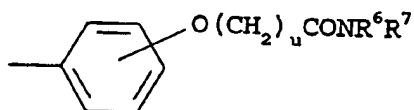
20 n is an integer of from 0 to 9; and
 R³ is hydrogen,
 straight, branched, or cycloalkyl of from
 3 to 10 carbons with from 0 to
 3 substituents selected from:

25 OH,
 OCH₃,
 CO₂R⁸,
 CONR⁸R⁹, or
 NHCONR⁸R⁹,

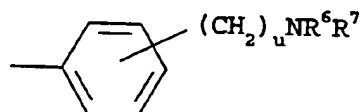
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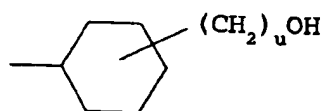


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, or

45



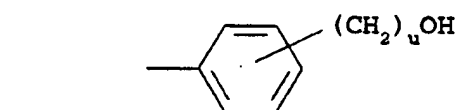
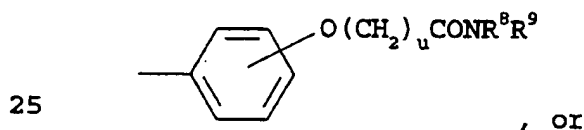
wherein u is an integer of from 0 to 3, R⁶
 and R⁷ are each independently hydrogen
 and methyl, R⁸ and R⁹ are each
 independently hydrogen and methyl.

4. A compound according to Claim 1 wherein:
 R¹ is cyclohexane,
 cyclopentane,
 methylcyclohexane,

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- 5 methylcyclopentane,
phenylethyl,
t-butyl,
2,2-dimethylpropane, or
2,2-dimethylpentane;
- 10 A when q, r and s are 0;
Ar¹ and Ar² are each phenyl;
X and Y are each independently selected from
-CONH- and -CH₂NH-;
n is an integer of from 3 to 8;
- 15 R³ is straight, branched, or cycloalkyl of from
3 to 9 carbons with 1 substituent selected
from:

- OH,
-OCH₃,
20 -CONR⁸R⁹,
-NHCONR⁸R⁹,



30

wherein u is an integer of from 0 to 3 and R⁸
and R⁹ are each independently selected
from hydrogen and methyl.

5. A compound selected from:

D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-
carbonyl]-L-phenylalanyl-N-(8-hydroxyoctyl)-
α-methyl-;

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- 5 D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-
carbonyl]-L-phenylalanyl-N-(9-amino-9-oxononyl)-
 α -methyl-, trifluoroacetate (10:7) salt;
- D-Phenylalaninamide, N-[(1,1-dimethylethoxy)-
carbonyl]-L-phenylalanyl-N-[4-(4-methoxyphenyl)-
10 butyl- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-dimethyl-
ethoxy) carbonyl]-L-phenylalanyl-N-
[3-(4-hydroxyphenyl)propyl]- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-
15 dimethylethoxy) carbonyl]-L-phenylalanyl- α -methyl-
N-3-methylbutyl-;
- DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl- α -methyl-
N-(5-phenylpentyl)-;
- 20 DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl-
N-cyclopentyl- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl-
25 N-(8-methoxyoctyl)- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl-
N-(7-carboxyheptyl)- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-
30 dimethylethoxy) carbonyl]-L-phenylalanyl-
N-[2-(acetylamino)ethyl]- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl-
N-(2-cyclopentylethyl)- α -methyl-;
- 35 DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl-N-[2-
(4-chlorophenyl)ethyl]- α -methyl-;
- DL-Phenylalaninamide, N-[(1,1-
dimethylethoxy) carbonyl]-L-phenylalanyl-
40 N-[(4-carboxycyclohexyl)methyl]- α -methyl-, trans-;

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DL-Phenylalaninamide, N-[(1,1-dimethylethoxy) carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(4-hydroxyphenyl) acetyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(cyclohexylmethoxy) carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(2-methylpropoxy) carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(3,4-dichlorophenyl) methoxy] carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(octahydro-2-naphthalenyl) oxy] carbonyl]-L-phenylalanyl- α -methyl-;

DL-Phenylalaninamide, N-[(1,1-dimethylethoxy) carbonyl]-L-phenylalanyl-3-chloro- α -methyl-;

D-Phenylalaninamide, 3-chloro-N-[(1,1-dimethylethoxy) carbonyl]-DL-phenylalanyl- α -methyl-;

Carbamic acid, [2-[[2-amino-2-oxo-1-(phenylmethyl) ethyl] amino]-1-(phenylmethyl) ethyl]-, 1,1-dimethylethyl ester;

D-Phenylalaninamide, N-[(1,1-dimethylethoxy) carbonyl]-L-phenylalanyl-N-[7-[(aminocarbonyl) amino] heptyl]- α -methyl-;

D-Phenylalaninamide, N-[(1,1-dimethylethoxy) carbonyl] L-phenylalanyl- α -methyl-N-[8-(methylsulfonyl) octyl];

(1-(1-[2-(4-Carbamoylmethoxy-phenyl)-ethyl carbamoyl]-1-methyl-2-phenyl-ethyl carbamoyl)-2-phenyl-ethyl)-carbamic acid tert-butyl ester;

D-Phenylalaninamide, N-[(1,1-dimethylethoxy) carbonyl]-L-phenylalanyl- α -methyl-N-[9-(methylamino)-2-oxononyl].

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6. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.
7. A method for treating central nervous system disorders in a mammal comprising administering the composition according to Claim 6 to said mammal.
8. A method for treating gastrointestinal disorders in a mammal comprising administering the composition according to Claim 6 to said mammal.
9. A method for treating respiratory disorders in a mammal comprising administering the composition according to Claim 6 to said mammal.
10. A method for treating inflammation disorders in a mammal comprising administering the composition according to Claim 6 to said mammal.
11. A method for treating circulatory insufficiency disorders in a mammal comprising administering the composition according to Claim 6 to said mammal.